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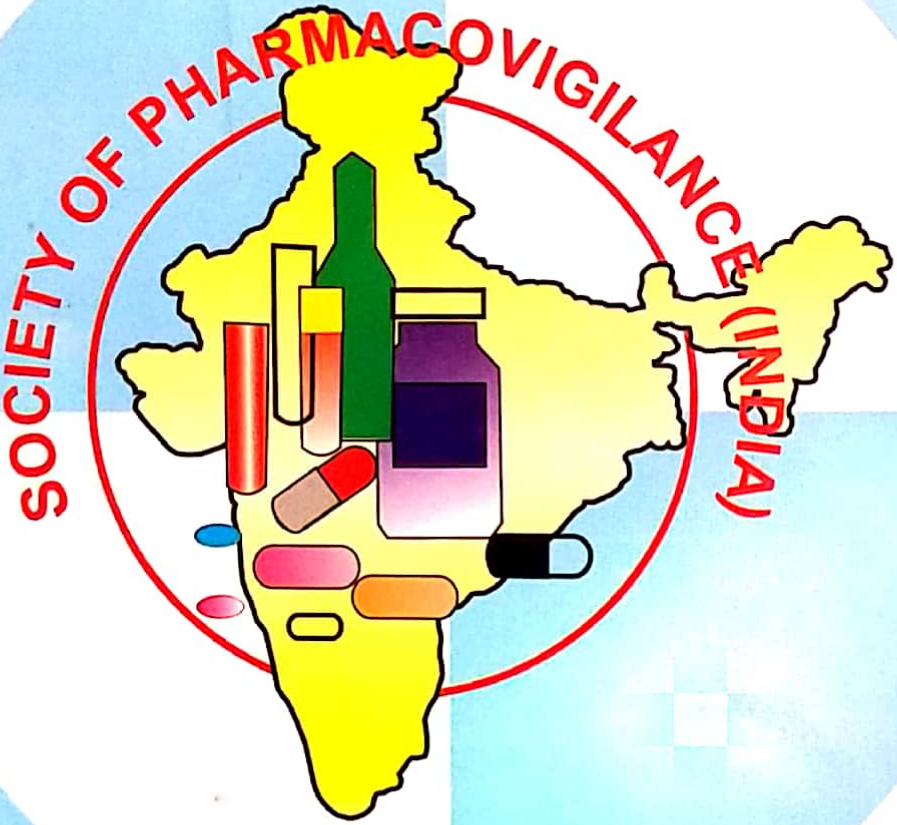

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Dr. Anurag Tomar

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Particulars

FROM THE DESK OF EDITOR

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.

India has more than half a million qualified doctors and15,000 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, 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.

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 Pharmacovigilance and drug safety is to collate data, analyze it and use the inferences to recommend informed regulatory interventions, besides communicating risks to healthcare professionals and the public.

Dr. Anurag Tomar
MBBS, MD (Pediatrics)
Editor in Chief

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REVIEW ARTICLE

Pharmacovigilance : A New Era for Herbal Safety

GOVIND MOHAN[1], SONIA SHARMA[1], SHRUTI TANDON[1], BHUPESH C. SEMWAL[1], NITIN AGRAWAL[2]

[1] *Institute of Pharmaceutical Research, G.L.A. University, Mathura - 281406 (India)*
[2] *College of Pharmacy, Agra - 282002 (India)*

ABSTRACT

According to WHO, "Herbal medicines include herbs, herbal materials, herbal preparations, and finished herbal products." In developing and underdeveloped countries, about 80% of the population depends on traditional system of medicine for primary health care. Traditional medicine practices have been adopted by different cultures and regions without having any specific standards and methods for estimating pharmacological/ therapeutic activity. The regulation of herbal medicine is difficult due to variations in the categorizations of traditional medicine therapies. If more than one herbal medicine is prescribed to the patient, there is always a risk of negative interactions. Out of many choices available in the market, the selection and use of the best and safest formulations for given individual requires considerable skill of the prescriber. The modern medicines have changed the path in which diseases are prevented and cured. However, despite of all their benefits, the evidence continues to mount that the adverse reactions to modern medicines are more common, may be preventable and sometimes causes death to the patient. In order to prevent or reduce harm to patients and thus improve public health, the traditional system of medicine urgently requires the methods for evaluating and monitoring the safety of such drugs in clinical use. Hence a well organized "Pharmacovigilance" system is required to regulate the safety and efficacy of the herbal medicines. However, the Department of *Ayush* is trying for their standardization and monitoring of ADR's, but these attempts will be more successful, if all the practitioners of these systems help in these efforts. The brief review of Pharmacovigilance in Indian system of medicine is discussed.

Keywords: Herbal Medicines, Pharmacovigilance, WHO

From prehistoric times, herbal medicine has been used by various communities and civilizations throughout the world. This trend is still continuing. For the past several decades, herbal medicines have been increasingly consumed by people without prescription. They are traditionally considered as harmless as they belong to natural sources. Herbal formulations which have reached widespread acceptability as therapeutic agents, such as antidiabetics,anti-arthritics,aphrodisiacs,hepatoprotectives, cough remedies, memory enhancers, adoptogens etc. However, with a more efficient case reporting of adverse drug reactions (ADR), the hazards of herbal medicines can be reduced. In this regard the World Health Organization (WHO) has set specific guidelines for the assessment of the safety, efficacy and quality of herbal medicines. The purpose of pharmacovigilance is to detect, assess, understand, and to prevent the adverse effects or any other possible drug-related problems, which is not only confined to chemical drugs, but extended to herbal, traditional, complementary medicines, biologicals, vaccines, blood products and medical devices[1]. Pharmacovigilance – an umbrella term used to describe the processes for monitoring and evaluating adverse drug reactions (ADR's) – is a key component of effective drug regulation systems, clinical practice and public health programmes[2].

Herbal pharmacovigilance should be implemented and pharmacovigilance centres should record apart from existing information with various aspects of the single herb and/or compound herbal formulations on concomitant use of chemical drugs, ADR's, delayed or acute toxic effects, allergies etc[1]. Pharmacovigilance involves the assessment of risks and benefits of medicines and plays a key role in pharmacotherapeutic decision making[1].

Brief History of Pharmacovigilance in India

Even though pharmacovigilance is still in its infancy, it is not new to India. It was not until 1986 that a formal adverse drug reaction (ADR) monitoring system consisting of 5 regional centers, each covering a population of 50 million, was proposed for India. However, nothing much happened until a decade later when in 1997, India joined the World

Health Organization (WHO) Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden[4].

The first multicentric study for monitoring ADR in Indian population was initiated on 1st April, 1989 with the financial assistance from Indian Council of Medical Research (ICMR). Five centers as First multicentric study were identified: J.N.Medical College, AMU, Aligarh; M.A.Medical College; All India Institute of Medical Sciences (AIIMS), New Delhi; L.L.R.M. Medical College, Meerut; Christian Medical College, Vellore. In this study, a total of 58194 patients were monitored for ADR during a period of three years, ICMR expert committee observed that the project has created awareness regarding ADRs in a section of medical community and has also resulted in training of staff in the monitoring of ADR's on the recommendation of expert committee, It was decided to extend the first multicentric study as a task force to different geographical regions of the country. Porf. K.C.Singhal continued as co-ordinator and Pricipal investigator for the ICMR programme for ADR monitoring[5,6]. Twelve centers of a second multicentric study: J.N.Medical College, AMU, Aligarh; Medical College, Baroda; Gandhi Medical College, Bhopal; L.T.M.Medical College, Sion, Mumbai; Guwahati Medical College, Guwahati; Osmania Medical College, Hyderabad; Govt. Medical College, Jammu; Chennai Medical College, Chennai; Maulana Azad Medical College, New Delhi; Medical College, Thiruvananthapuram; St. John's Medical College, Bangalore; Christian Medical College, Vellore[7].

The National Pharmacovigilance Program established in January 2005, was to be overseen by the National Pharmacovigilance Advisory Committee based in the Central Drugs Standard Control Organization (CDSCO), New Delhi. Two zonal centers-the South-West zonal centre (located in the Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai) and the North-East zonal centre (located in the Department of Pharmacology, AIIMS, New Delhi), were to collate information from all over the country and send it to the Committee as well as to the Uppsala Monitoring centre in Sweden. Given this background on pharmacovigilance in India to date, nearly two decades later from its origin in 1986, things have definitely changed for the better but at a very slow pace. The Regulatory Authority for India should be commended for introducing and implementing the Schedule Y and for reporting all serious adverse events (SAEs) including suspected unexpected serious adverse reactions (SUSARS) from clinical trials[4].

The United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) defines pharmacovigilance as "the process of (a) monitoring medicines as used in everyday practice to identify previously unrecognized or changes in the patterns of their adverse effects; (b) assessing the risks and benefits of medicines in order to determine what action, if any, is necessary to improve their safe use; (c) providing information to users to optimize safe and effective use of medicines; (d) monitoring the impact of any action taken[8].

WHO defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

Recently,the WHO Concerns have been widened to Include:

- Herbals, traditional and complementary medicines, blood products, biological, medical devices, vaccines.
- And the WHO also desires to include other issues like:
- Substandard medicines, medication errors, lack of efficacy reports, use of medicines for indications that are not approved and for which there is inadequate scientific basis, case reports of acute and chronic poisoning, assessment of drug-related mortality, abuse and misuse of medicines, adverse interactions of medicines with chemicals, other medicines and food[9].

Why Pharmacovigilance is Required for 'Natural' Drugs ?

The use of herbal and traditional medicines raises concerns in relation to their safety. There is wide misconception that 'natural' means 'safe' and even the chronic use of a medicine, based on tradition, and assures both its efficacy and safety. There are examples of traditional and herbal medicines being adulterated or contaminated with allopathic drugs like corticosteroids, NSAIDs and heavy metals. Many traditional medicines are manufactured for global use and they have moved beyond the traditional and cultural framework for which they were originally intended. Self-medication of traditional drugs further aggravates the risk to patients. When traditional and herbal medicines are used in conjunction with other medicines, there is the potential risk of ADRs. As with other products intended for human use (drugs, dietary supplements and

foods), herbal drugs should be incorporated within a regulatory framework. These products should be governed by standards of safety, quality and efficacy, which are equivalent to those required for other pharmaceutical products. Difficulties in achieving this arise from the growth of an ambiguous zone between foods and medicines, into which an increasing number of herbal products fall. The regulatory status of herbal products differs significantly from country to country[10]. Around 110 countries regulate herbal medicine in response to a dramatically increased use globally and demand for more vigorous requirements to ensure quality, safety and efficacy[11]. These disparities in regulation between countries have serious implications for international access and distribution of such products. For instance, in one country a herbal product may be obtainable only on prescription and from an authorized pharmacy, whereas in another country, it may be obtainable from a health food shop, or even, as has become common practice, by mail order or Internet.

For all these reasons, inclusion of herbal and traditional medicines in national pharmacovigilance programmes has become important and inevitable. Healthcare providers, including traditional health practitioners, regulators, manufacturers and the public share a responsibility for their informed and safe use. The WHO has produced guidelines for assessment of the safety, efficacy and quality of herbal medicines. New systematic approaches for monitoring the safety of plant-derived medicinal products are being developed. A number of national pharmacovigilance centres are now monitoring the safety of traditional medicines. Therefore to succeed, getting the collaboration and support of consumers, traditional health practitioners, providers of traditional and herbal medicines and other experts is necessary. More attention needs to be given to research and to training of healthcare providers and consumers in this area[10]. Department of AYUSH recognized Institute for Postgraduate Teaching Research in Ayurveda, Gujarat Ayurveda University, Jamnagar as National Pharmacovigilance Resource Centre for Ayurveda, Siddha and Unani drugs (NPRC-ASU) on 20th August 2008 under the Department of AYUSH, Ministry of Health and Family welfare, Government of India.

Since the Physicians of Indian Systems of Medicine have learnt the art and science of their medicine in Sanskrit, Hindi, Arabic/ Persian or in regional languages as the case may be and they understand ADR Terminology in their languages, need was felt to provide ADR dictionary of WHO centre for International Drug Monitoring Uppsala, Sweden. As a first step in this direction Prof. KC Singhal translated ADR Dictionary of UMC in Hindi which was published by Society of Pharmacovigilance, India. Department of AYUSH is critically evaluating the translation and plans to bring out this second edition[12].

Examples of Adverse Effects of Herbs

Adverse effects of herbal remedies may be caused by the pharmacologic activity of the constituents or by intrinsically toxic components, overdose (acute or chronic), interactions between herbal remedies or herb-drug interactions and various other Rasashastra factors. The few examples of ADR's by herbs are:

- Sassafras albidum (Safrole) is used as carminative and for gout, rheumatic pain, and dermatologic conditions. Studies in mice with high doses of the aqueous or ethanolic extracts have resulted in ataxia, central nervous system depression and hypothermia.
- Hypericum perforatum and Angelica archangelica have been reported to cause photosensitivity at much higher doses than normally used therapeutically.Herbal laxatives, such as seena or cascara, are popular remedies for constipation. As well as having laxative properties, these may cause abdominal pains.
- Anaphylaxis and allergic reactions are the most common reports to the UMC. Herbs suspected to be associated with these types of reprts include asparagus root, silymarin, bromelain, Echinacea, fennel oil, fenugreek seed, garlic, ginkgo biloba, psyllium mucilage and ispaghula[13].
- Cytochrome P450 (CYP P450) enzymes are a superfamily of mono-oxygenases that are found in all kingdoms of life. The CYP P450 enzymes constitute a large superfamily of haem-thiolate proteins involved in the metabolism of a wide variety of both exogenous and endogenous compounds. The CYP activities have been shown to be involved in numerous interactions especially between drugs and herbal constituents. The majority of serious cases of drug interactions are as a result of the interference of the metabolic clearance of one drug by yet another co-administered drug, food or natural product. Gaining mechanistic knowledge towards such interactions has been accepted as an approach to avoid adverse reactions. The inductions and inhibition of CYP enzymes by natural products in the presence of a prescribed drug has led to adverse effects.

Herbal medicines such as St. John's wort (Hypericum perforatum), garlic (Allium sativa), piperine (from Piper sp.), ginseng (Ginseng sp.), gingko (Gingko biloba), soya beans (Glycine max), alfalfa (Medicago sativa) and grape fruit juice show clinical interactions when co-administered with medicines[14].(Table 1)

How does Pharmacovigilance operate?

Table 1: Herbal- Drug Interactions and their Mechanism[10].

S. No.	Medicinal plant	Herbal constituent and chemical formula	Drug	Experimental model	CYP enzyme involved (isoform)	Symptom of interaction	Mechanism
1	St. John's wort (Hypericum Perforatum)	Hyperforin C35H52O4	Ciclosporin	Human Hepatocytes	CYP3A4, 2E1, 2C19	Reduction in serum	Induce activity of CYP 1A , 2B
2.	St. John's wort (Hypericum perforatum)	Hyperforin C35H52O4	Warfarn	Human clinical trail	CYP3A4	Loss of anticoagulant activity	Inhibition of CYP activity
3.	St. John's wort (Hypericum perforatum)	Hyperforin C35H52O4	Omeprazole	Human clinical trail	CYP2C19	Decreases Plasma concentration	Induction of CYP2C19 , 3A4
4.	Garlic (Allium sativum)	Allicin C6H10OS2	Sequinavir	Human clinical trail	CYP3A4	Reduction of hypertension	Inhibition of CYP2C9, 2C19, 3A4
5.	Garlic (Allium sativum)	Allicin C6H10OS2	Sequinavir	Human clinical trail	CYP2C9, 2C19	Reduction of hypertension and hyperlipidameia	Inhibition of CYP2C9, 2C19
6.	Black Pepper (Piper nigrum)	Piperine C17H19NO3	Antimicrobial	In vivo studies in rat	CYP2E1	suppressed CYP2E1 expression	Induce activity of CYP 1A , 2B
7.	Ginseng (Panax ginseng)	Ginsenoside C42H72O14 , Ginsenoide	Phenelzine	In vitro studies in mouse and human microsomes	CYP2E1	Induce CYP3A4, 2D6,2C19, 2C9 activity	Inhibition of CYP2E1 activity
8.	Gingko (Gingko biloba)	Ginkgolic acid C22H34O3	Diltiazem	In vitro and in vivo analysis on rat hepatic and intestinal CYP enzymes	CYP3A, 2B	Inhibit metabolism of Diltiazem (drug)	Induces CYP2B and inhibit CYP1A2, C9 2C19

The WHO International Drug Monitoring Programme

Under the WHO International Drug Monitoring Programme, national pharmacovigilance centres designated by the competent health authorities are responsible for the collection, processing and evaluation of case reports of suspected adverse events/reactions supplied by health-care professionals (mainly spontaneous reporting by physicians of reactions associated with the use of prescribed medicines).

UMC manages the global WHO database to which all case reports received by the national pharmacovigilance centres are sent using vigibase online.UMC uses the global WHO database to identify/detect signals of new adverse reactions from the cumulative data and to communicate risk assessments back to the national pharmacovigilance centres and to others concerned with drug safety.

The core functions in this collaborative international programme can be summarized as follows.

a) Functions of National Pharmacovigilance Centres:

- Continuous collection of reports of suspected adverse reactions for medicines on the market
- Assessment of case reports in respect of:
- Quality of documentation
- Causality assessment
- Coding to international standards using the appropriate medicine classification (the anatomical-therapeutic-chemical (ATC) classification), adverse reaction classification (WHO Adverse Reaction Terminology (WHO-ART)) and the Medical Dictionary for Drug Regulatory Activities (MedDRA)
- Clinical relevance
- Quality control, in particular identification of duplicate reports
- Transmission in suitable format of the assessed reports to UMC
- Generation of hypotheses or the identification of signals. These activities may be strengthened by a search of the global WHO database (managed by UMC) for similar reports
- Communication of relevant safety information to the national and regional regulatory authorities, health professionals, pharmaceutical companies and other players as appropriate
- Further investigation of signals, risk factors or pharmacological mechanisms
- Receipt and communication as appropriate of safety information resulting from analyses by UMC and from regulatory agencies, case reports and the literature
- Provision of feedback to reporters
- Timely advice to health-care professionals and consumers on drug safety issues
- Education and training
- Information sharing at regional and global levels.

b) Functions of the Uppsala Monitoring Centre UMC:

- Receipt and storage of reports from national pharmacovigilance centres.
- Provision of facilities to enable national pharmacovigilance centres to search the global WHO database.
- Generation of signals from the global WHO database.
- Communication of signal analyses to national pharmacovigilance centres and clinical review of the analyses by experts.
- Provision of technical assistance to national pharmacovigilance centres.
- Facilitation of communication between countries.
- Maintenance and development of WHO-ART and the use of MedDRA within the WHO International Drug Monitoring Programme.
- Training of national pharmacovigilance centre personnel.
- Standardization of procedures relating to pharmacovigilance activities.
- Publication of relevant documents.
- Provision of data as appropriate to other parties.
- Among the many players that need to be involved in pharmacovigilance systems at different levels are: qualified health professionals such as providers of medicines (physicians, dentists, pharmacists) and nurses, researchers and academics, media writers, the pharmaceutical industry, national and regional drug regulatory authorities, patients/consumers, lawyers, poison centres, drug information centres, and international and regional health organizations
- In collaboration with UMC, national Pharmaco-

vigilance centres have already achieved a great deal in the following areas:

- Collecting and analysing case reports of adverse drug reactions.
- Distinguishing signals from "background noise".
- Making regulatory decisions based on strengthened signals.
- Alerting prescribers, manufacturers and the public to new risks of adverse reactions[9].

Pharmacovigilance of Herbal Drugs

In herbal medicines where the active ingredients have been identified, the preparation of these medicines should be standardized to contain a defined amount of the active ingredients, if adequate analytical methods are available. In cases where it is not possible to identify the active ingredients, the whole herbal medicine may be considered as one active ingredient[15].

Botanical Verification and Quality Consideration

UMC has reconstructed the management of data relating to herbal products. The herbal anatomical–therapeutic-chemical classification (HATC) based on botanical science, pharmacognosy, phytochemistry, literature search and documented traditional use rather than chemistry and evidence-based medicine have been introduced. The HATC classification indicates a) suggested anatomical site of Pharmacological action and b) range of intended medical uses including traditional therapeutic uses.

The new structure and classification of herbal substances (entities) within the global WHO database will facilitate finding information about finished herbal products containing a specified medicinal plant or just a specific part, herbal materials, or extract of other herbal preparations of the specified medicinal plant.

Substitution of herbs in Unani and Ayurvedic system of medicine has been permitted for many decades. The necessity for which might have arisen due to lack of availability in a particular region or a particular season. In Unani system of medicine substitution is permitted for all drugs whether single ingredient or multiple ingredient formulation. Whereas, in Ayurveda the main drug in any formulation is not substituted, however, other groups in the formulation can be substituted by appropriate Pratinidhi drug[16,17].

a) Research and Evaluation of Safety and Efficacy

Research and evaluation of herbal medicines without a long history of use or which have not been previously researched should follow WHO's Research guidelines for evaluating the safety and efficacy of herbal medicines. For herbal medicines with a well-documented history of traditional use, the following procedures for conducting research and evaluating safety and efficacy may be followed.

b) Literature Review

In assessing the safety and/or efficacy of a herbal medicine, whether derived from a single plant or from a defined mixture of plants, the first step involves the evaluation of literature reports. The literature search should include reference books, review articles, systematic surveillance of primary sources, and/or database searches. It should be kept in mind, however, that reference books and review articles might contain inaccurate information. Nevertheless, these sources will cite primary references that can be consulted for in-depth analysis. The search profile used should be recorded, as should details of any references cited, whether or not they are available. The literature search should then be extended to gather information on closely related plant species for chemotaxonomic correlation. If several investigators publish similar safety and/or efficacy data, they should be accepted as useful indicators. In vitro (biochemical or cellular) safety data should be viewed as indicators of potential toxicity, but not as absolute markers. In vivo data from animal studies are more indicative of toxicity and may be considered to be safety markers. For both safety and efficacy, a pharmacological effect observed in vitro or in animal, models is not necessarily applicable to humans. In vitro data usually serve to verify the reported mechanism of action in animals or humans. Such data have to be confirmed by clinical studies. Well-documented reports of pharmacological activity in animals or humans may be viewed as having scientific rationale.

Review of Safety and Efficacy Literature

A review of the literature should identify the current level of evidence for the safe and effective use of a herbal medicine. The study design should be evaluated, taking note of, for example, the number of patients, specific diagnosis, dosage, duration of administration, criteria for evaluation (such as improvement of symptoms), absence of simultaneous therapy, and valid statistical analysis. In

cases where traditional use and experience of an herbal medicine in humans have not established its safety and efficacy, new clinical studies will be necessary. If well-known herbal medicines are formulated into a new mixture, however, the requirements for proof of safety and efficacy should take into account the well established uses of each herbal medicine. Such information may appear in authoritative national documents (such as pharmacopoeias or official guidelines of national authorities) or in highly respected scientific publications.

a) Safety of Herbs

Reported and documented side-effects (recorded according to established principles of pharmacovigilance) of a herb or herb mixture, its closely related species, constituents of the herb and its preparations/finished herbal products should be taken into account when decisions are made about the need for new pharmacological or toxicological studies.

Tests which examine effects that are difficult or even impossible to detect clinically should be encouraged. Suggested tests include immunotoxicity (e.g. tests for allergic reactions), genotoxicity, carcinogenicity and reproductive toxicity. WHO's Research guidelines for evaluating the safety and efficacy of herbal medicines can also be consulted for these as well as for other appropriate toxicity tests. Only when there is no documentation of long historical use of a herbal medicine, or when doubts exist about its safety, should additional toxicity studies be performed.

Where possible, such studies should be carried out in vitro. Using in vitro tests can reduce the number of in vivo experiments. If in vivo studies are needed, they are to be conducted humanely, with respect for the animals' welfare and rights. Toxicity studies should be conducted in accordance with generally accepted principles, such as those described in WHO's Research guidelines for evaluating the safety and efficacy of herbal medicines.

b) Efficacy of Herbs

It is important for herbal medicines, and particularly for those made from mixture herbal products, that the requirements for proof of efficacy, including the documentation required to support the indicated claims, should depend on the nature and level of the indications. For the treatment of minor disorders, for nonspecific indications, or for prophylactic uses, less stringent requirements (e.g. observational studies) may be adequate to prove efficacy, especially when the extent of traditional use and the experience with a particular herbal medicine and supportive pharmacological data are taken into account. The level of the evidence and the grading of recommendations must correspond to the nature of the illness to be treated or the nature of the physical or mental function to be influenced and regulated[15].

Pharmaco-Epidemiological Methods used in Pharmacovigilance

Pharmacoepidemiology is the science concerned with the benefit and risk of drugs used in populations and the analysis of the outcomes of drug therapies. The data for pharmacoepidemiological investigations are commonly derived from case-control studies, cohort studies, and randomized clinical trials.

A case report describes the particular outcome or experience of a person who has been exposed to a drug. These reports are useful for generating hypotheses about the effects of the drug, and may lead to further studies to test these hypotheses. A case series reports on two or more people with common exposure to a drug, or a common outcome.

In a case-control study a number of people are selected based on the presence (cases) or absence (controls) of an adverse event. The investigators then attempt to establish a causal relationship between the presence (and absence) of the event and prior exposure to one or more suspected drugs.

In cohort studies, two groups of people representing those exposed and those not exposed (controls) to a drug are identified and observed over a period of time. The incidences of the adverse reactions in both groups are compared.

Randomized clinical trials (RCTs) are experimental studies in which the investigator controls the therapy that is to be received by each participant. Patients are randomly allocated to the control or exposed group. The major strength of RCTs is that bias and any confounding factors are removed if an RCT is well executed. RCTs are normally used to investigate the clinical efficacy of drugs; however, when used as a pharmacovigilance tool, the measured outcome is the presence or absence of an adverse reaction[10].

Conclusion

Herbal medicines are referred as "Phytomedicine" or "botanical medicine". In approximately 40-year history, the pharmacovigilance remains a dynamic clinical as well as scientific field. It continues to play an important role in order to meet the challenges which are posed by the ever increasing therapeutic jungle, which carry an inevitable and sometimes it will be an unpredictable potential for harm. When adverse effects and toxicity do appear from the sides of herbal interactions or from herbal medicines, then it become essential that these must be reported, analyzed and their significance should be communicated effectively to the consumer that has the knowledge to interpret the information.

"Pharmacovigilance is needed for the prevention of drug-induced human suffering and to avoid financial risks associated with unexpected adverse effects. Therefore, it can be said that medicines on the market need continuous monitoring in every country[17]".

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REVIEW ARTICLE

Drug Utilization Studies

UMA ADVANI, SHOBHA KULSHRESHTHA

Department of Pharmacology
NIMS Medical College & Hospital, Nims University,Shobha Nagar, Jaipur - 303121 (India)

ABSTRACT

Drug utilization study seeks to monitor, evaluate and, if necessary, suggest modification in prescribing practices of medical practitioners with the aims of making medical care rational and cost effective. Irrational drug use is a common problem worldwide. The constantly increasing number of medicines and treatment options serves to increase the irrational medicine treatment encounters that ultimately lead to poor patient outcome and significant wastage of money and resources. The impact of inappropriate medicine use on the healthcare system is reduction of quality of medicine therapy leading to increased morbidity and mortality, increased cost of therapy and increased risk of unwanted effects such as adverse medicine reaction. Ineffective inappropriate and economically nonviable use of medicines is often observed in health care throughout the world. This is more often in the developing countries. The need for achieving quality use of medicines in the healthcare system is not only because of the financial reasons with which policy makers and administrators are usually most concerned. Appropriate use of drugs is also one essential element in achieving quality of health and medical care for patients and the community as a whole. These studies are useful to provide denominators to calculate rates of reported adverse drug reactions, to monitor the utilization of drugs from therapeutic categories where particular problems can be anticipated (*e.g.*, narcotic analgesics, hypnotics and sedatives, and other psychotropic drugs), to monitor the effects of informational and regulatory activities (*e.g.*, adverse events alerts, monitoring urgent safety restrictions). Drug utilization data may be used to produce crude estimates of disease prevalence (*e.g.*, cardiovascular disease, antidiabetic drugs), to plan drug importation, production, and distribution, and to estimate drug expenditures.

Key Words: Drug Utilization, Rational Drug Use, Irrational Drug Use, Adverse Drug Reactions

Introduction

Drugs are a valuable resource in developing countries and in view of their scarcity, often considered an indicator of quality of care. Worldwide, the reliable supply of pharmaceuticals alone is often used as a criterion for quality of care. Obviously, the reliable supply of pharmaceuticals, implying effective management of drug supply should not be the only indicator that characterizes a high standard of care. Without an evaluation of the actual use of the pharmaceuticals the indicator is incomplete. In fact, critics assert that the failure to recognize and appreciate the appropriate use of drugs by both the patient and the provider will undermine any positive effect that a reliable supply of drugs may have.[1] Consequently, the Action Programme on Essential Drugs at the WHO and the International Network for the Rational Use of Drugs (INRUD) have collaborated on methods to systematically identify inappropriate drug use and implement and evaluate interventions to promote appropriate drug use (WHO 1993).

With the increasing quantity and variety of pharmaceuticals available today in both developed and developing countries, their potential inappropriate use is a growing concern. Not only the health risks associated with inappropriate drug prescription but also the economic cost to facilities and patients must be considered. As a result, strategies to identify, resolve and prevent inappropriate pharmaceutical use have been the topic of numerous articles, conferences and studies.[2]

Aim of Drug Utilization Studies

The principal aim of drug utilization research is to facilitate rational use of drugs in populations. For the individual patient rational use of a drug implies the

prescription of a well-documented drug in an optimal dose on the right indication, with the correct information and at an affordable price. Without knowledge on how drugs are being prescribed and used, it is difficult to initiate a discussion on rational drug use and to suggest measures to change prescribing habits for the better.

Development of Drug Utilization Research

The development of drug utilization research was sparked by initiatives taken in Northern Europe and the United Kingdom in the mid-1960s[1,4]. The pioneering work of Arthur Engel in Sweden and Pieter Siderius in Holland [5] alerted many investigators to the importance of comparing drug use between different countries and regions. Their demonstration of the remarkable differences in the sales of antibiotics in six European countries between 1966 and 1967 inspired WHO to organize its first meeting on Drug consumption in Oslo in 1969 [6]. This led to the constitution of the WHO European Drug Utilization Research Group (DURG).

The pioneers of this research understood that a correct interpretation of data on drug utilization requires investigations at the patient level. It became clear that we need to know the answers to the following questions:

- Why drugs are prescribed.
- Who are the prescribers.
- For whom the prescribers prescribe.
- Whether patients take their medicines correctly.
- What are the benefits and risks of the drugs.

Drug utilization research was defined by WHO in 1977 as "the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences". Since then, a number of other terms have come into use and it is important to understand the interrelationships of the different domains.

Epidemiology is defined as "the study of the distribution and determinants of health-related states and events in the population, and the application of this study to control of health problems". A suitable definition of pharmacoepidemiology is : The study of the use and effects or side effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in the population thereby improving health outcomes. Pharmacoepidemiology applies epidemiological methods to studies of the clinical use of drugs in populations.

Pharmacosurveillance and pharmacovigilance are terms used to refer the monitoring of drug safety such as spontaneous adverse effect reporting systems, case-control and cohort studies. Pharmacoepidemiology may be drug-oriented, emphasizing the safety and effectiveness of individual drugs or groups of drugs, or utilization-oriented aiming to improve the quality of drug therapy through pedagogic intervention.

Drug utilization research may also be divided into descriptive and analytical studies. The emphasis of the former has been to describe patterns of drug utilization and to identify problems deserving more detailed studies. Analytical studies try to link drug utilization data to figures on morbidity, outcome of treatment and quality of care with the ultimate goal being to assess whether drug therapy is rational or not. Sophisticated utilization-oriented pharmacoepidemiology may focus on the drug (e.g., dose-effect and concentration-effect relationships), the prescriber (e.g., quality indices of the prescription), or the patient (e.g., selection of drug and dose versus kidney function, drug metabolic phenotype or genotype, age, etc).

Drug utilization research is thus an essential part of pharmacoepidemiology as it describes the extent, nature and determinants of drug exposure. In common use, the distinction between these two terms has become less sharp, and they are sometimes used interchangeably. However, while drug utilization studies often employ various sources of information focusing on drugs, e.g., aggregate data from wholesale and prescription registers. The term epidemiology implies defined populations and that drug use can be expressed in terms of incidence and prevalence.

Drug utilization research and pharmacoepidemiology may provide insights into the following aspects of drug use and drug prescribing:

i. Pattern of use: extent and profiles of drug use and trends in drug use and cost over time.

ii. Quality of use: audits comparing actual use to national and regional prescription guidelines or local drug formularies. Quality indices of drug use may include the choice of drug (compliance to recommended assortment), drug cost (compliance to budgetary recommendations), drug dosage (awareness of inter-individual variations in dose requirements and age dependence), drug interaction awareness, ADR awareness, proportion of patients being

aware of/unaware of the cost/benefit of the treatment, etc.

iii. Determinants of use: user characteristics (e.g. socio-demographic parameters, attitude towards drugs), prescriber characteristics (e.g. specialty, education and factors influencing therapeutic decisions), and drug characteristics (e.g. therapeutic properties, affordability)

iv. Outcomes of use: health outcomes (benefits and adverse effects) and economic consequences.[7,8]

Need of Drug Utilization Studies

Drug utilization study seeks to monitor, evaluate and, if necessary, suggest modification in prescribing practices of medical practitioners with the aims of making medical care rational and cost effective. Irrational drug use is a common problem worldwide. The constantly increasing number of medicines and treatment options serves to increase the irrational medicine treatment encounters that ultimately lead to poor patient outcome and significant wastage of money and resources. The impact of inappropriate medicine use on the healthcare system is reduction of quality of medicine therapy leading to increased morbidity and mortality, increased cost of therapy and increased risk of unwanted effects such as adverse medicine reaction.

Especially, in a developing country like India, irrational prescribing is a common finding. Realizing the importance of drug utilization studies in building a safe and effective healthcare system, various countries have made drug utilization review boards to provide information on drug utilization data at national level. In India, several research groups have initiated efforts to study the drug utilization patterns mostly in the last two decades. Most of these groups are from the pharmacology departments of medical institutions, pharmacy colleges, newly established pharmacy practice departments and other agencies. The data emerging from these studies has provided insight into various aspects of drug utilization across the country. This has led to useful initiatives like educating on the idea of restricting the sale of antibiotics etc. Most of these drug utilization studies have adopted a very sound methodology, which decides the usefulness of the outcome. The authors have also noted that the results presented in some scientific meetings do not seem to follow an appropriate methodology and as a result, the efforts spent in conducting these studies do not take one anywhere. Though the intention of the researchers is honest and purposeful, it is probably the unawareness of established protocols on the part of researchers which leads to such situations.[9]

Drug utilization research in itself does not necessarily provide answers, but it contributes to rational drug use in three important ways:

A. Description of drug use patterns

Drug utilization research will increase our understanding of how drugs are being used by:

- Making estimates of the numbers of patients exposed to drugs within a given time period.
- Describing the extent of use at a certain moment and/or in a certain area (e.g. country, region, community, hospital).
- Estimating (e.g. on the basis of epidemiological data on a disease) to what extent drugs are properly used, overused, or underused.
- Describing the pattern or profile of drug use - assessing which alternative drugs are being used for particular conditions and to what extent.
- Comparing observed patterns of drug use with current recommendations or guidelines for the treatment of a certain disease.
- Applying quality indicators to drug utilization patterns.
- Feed back drug utilization data to prescribers.
- Relating the number of case reports about a drug problem or adverse effects to the number of patients exposed in order to assess the potential magnitude of the problem.

B. Early Signals of Irrational use of Drugs

Drug utilization research may generate hypotheses that set the agenda for further investigations by:

- Comparing drug utilization patterns and costs between different regions or time periods.
- Comparing observed patterns of drug use with current recommendations or guidelines for the treatment of a certain disease.

C. Interventions to improve drug use – follow-up

Drug utilization research may enable us to assess whether interventions undertaken to improve drug use have the desired impact by:

- Monitoring and evaluating the effects of measures taken to improve undesirable patterns of drug use (regional or local formularies, information campaigns, regulatory policies, etc.)
- Following the impact of regulatory changes or changes in insurance or reimbursement systems. This also requires a broad survey, because the total cost to society may remain the same or may even increase, if other more expensive drugs are used as an alternative.
- Assessing to which extent promotional activities of the pharmaceutical industry and educational activities of the society impact on the patterns of drug use.[9]

Types of Drug Use Information

Different types of drug use information are required depending on the problem being evaluated. These include information about the overall drug use, or use of drug groups, individual generic compounds or specific products. Often, information about the condition being treated, about the patient and about the prescriber will be required. In addition, data on drug costs will be important in ensuring that drugs are used efficiently and economically. These types of drug information are described below:-

A. Drug Based Information

The trends in total drug use may sometimes be useful to know, but more detailed information is usually required to answer clinically important questions. This may involve aggregation of drug use at various levels, and information on indications, doses and dosage regimens.

B. Problem or Encounter-Based Information

Instead of asking how a particular group of drugs is used, one may well address the question how a particular problem (e.g. sore throat, hypertension, gastric ulcer, depression) is managed.

C. Patient Information

Demographic and other information about the patient will often be useful. The age distribution of patients will sometimes be of critical importance, for example to assess the likelihood of severe adverse effects with NSAIDs (Non-steroidal anti-inflammatory drugs), or whether the drug is being used in an age group different to that in which the clinical trials were performed. The co-morbidities of the patient group may be important in determining treatment choice and adverse effects. As an example in the management of hypertension, beta-blockers should be avoided in patients with asthma, and ACE inhibitors preferred in patients with heart failure. Qualitative information such as knowledge, beliefs, and perceptions among patients and their attitudes to drugs will be important in some cases, for example in assessing patient pressures on doctors to prescribe antibiotics, or in designing consumer information or education programs.

D. Prescriber Information

The prescriber is a critical point in determining drug use. Some skeptics even claim that doctors differ more than patients and those differences in drug prescribing often lack rational explanations. Dissecting the factors that determine prescribing behavior is therefore often central to understanding how and why drugs are prescribed.[3]

Sources of Drug Utilization Data

The drug use chain includes the processes of drug acquisition, storage, distribution, prescribing, patient compliance and review of outcome of treatment. Each of these events is an important aspect of drug utilization. Drug utilization data may be derived from

- Quantitative study
- Qualitative study

Quantitative data may be used to describe the present state, and trends in drug prescribing and drug use at various levels of the health care system. Quantitative data are usually obtained from routinely collected data or from surveys. Qualitative studies assess the appropriateness of drug utilization and generally link prescribing data to reasons (indications) for prescribing. Such studies have been referred to as Drug Utilization Review or Drug Utilization Evaluation. The process is one of a "therapeutic audit" based on defined criteria and has the purpose of improving the quality of therapeutic care. There is an increasing interest in the evaluation of the economic impact of clinical care and medical technology. This has evolved into a discipline dedicated to the study of how

pharmacotherapeutic methods influence resource utilization in health – pharmacoeconomics.[10]

Factors Affecting Drug Utilization

Numerous factors, many of which are interrelated, may affect drug expenditure, utilization, and ultimately health outcomes. Some of these factors are presented (Table 1) in these factors present important challenges for the development of indicators to monitor trends and results that affect not only the performance of the health care system, but also the health of the population.

Antibacterials and Drug Utilization Studies

The word antibiotic comes from the Greek anti meaning 'against' and bios meaning 'life' (a bacterium is a life form).' In common usage, an antibiotic (from the Ancient Greek:

Table 1: Factors Affecting Drug Utilization

1. Prices	
2.Entry of New Drug Chemicals	
3. Volume of Drug Use	
4. Population-related	Changes in population demographics. Age, gender and ethnicity. Changes in health status of a population. Emergence of new diseases. Epidemics.
5. System-related	Changes and transition associated with health system reform and restructuring. Move towards shorter hospital stays and home or community care (shift of drug provision from hospital to community). Changes in policies and programs. The extent of formulary listings. Eligibility and co-payments. Availability of third party insurance coverage.
6. Research and technology-related (clinical and informational)	New treatment approaches. Drugs replacing surgery. Drug therapy for previously untreatable diseases. Availability of more and/or improved diagnostic technology. Outcomes research, evidence-based preventive or curative approaches in diagnosis or treatment. Use of programs and technology in monitoring patients. Pharmaceutical industry. Development of new drug products (e.g., new strengths, new drug forms and presentations). Promotion of drugs to physicians. Drug sampling. Direct to consumer advertising.
7. Practice and people-related (health care providers and consumers)	Changes in prescribing and dispensing practices. Number and mix of prescribers (specialists, general practitioners, nurse practitioners and doctors). Multiple doctoring. Consumers' expectations and behaviors. Wastage.[11]

ἀντί – anti, "against", and βίος – bios, "life") is a substance or compound that kills bacteria or inhibits its growth.[12] Antibiotics belong to the broader group of antimicrobial compounds, used to treat infections caused by microorganisms, including fungi and protozoa.

The term "antibiotic" was coined by Selman Waksman in 1942 to describe any substance produced by a microorganism that is antagonistic to the growth of other microorganisms in high dilution.[13] This original definition excluded naturally occurring substances that kill bacteria but are not produced by microorganisms (such as gastric juice and hydrogen peroxide) and also excluded synthetic antibacterial compounds such as the sulfonamides. Many antibiotics are relatively small molecules with a molecular weight less than 2000 Da.[14]

What are Antibiotics for ?

An antibiotic is given for the treatment of an infection caused by bacteria. They target only bacteria - they do not attack other organisms, such as fungi or viruses. If you have an infection it is important to know whether it is caused by bacteria, and not a virus or fungus. Most upper respiratory tract infections, such as the common cold and sore throats are generally caused by viruses - antibiotics do not work against viruses. If antibiotics are overused or used incorrectly there is a chance that the bacteria will become resistant - the antibiotic becomes less effective against that type of bacterium. A broad -spectrum antibiotic can be used to treat a wide range of infections. A narrow - spectrum antibiotic is only effective against a few types of bacteria. There are antibiotics that attack aerobic bacteria, while others work against anaerobic bacteria. Aerobic bacteria need oxygen, while anaerobic bacteria don't.

Antibiotics may be given beforehand, to prevent infection, as might be the case before surgery. This is called 'prophylactic' use of antibiotics. They are commonly used before bowel and orthopedic surgery.[15]

Rational Drug Use

Ineffective inappropriate and economically nonviable use of medicines is often observed in health care throughout the world. This is more often in the developing countries. The need for achieving quality use of medicines in the healthcare system is not only because of the financial reasons with which policy makers and administrators are usually most concerned. Appropriate use of drugs is also one essential element in achieving quality of health and medical care for patients and the community as a whole.

WHO Defined: "Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and the lowest cost to them and their community." (WHO, 1985)

The definition implies that rational use of drugs, especially rational prescribing should meet following criteria's:

Appropriate Indication: The decision to prescribe drug(s) is entirely based on medical rationale and that drug therapy is an effective and safe treatment.

Appropriate Drug: The selection of drugs is based on efficacy, safety, suitability and cost considerations.

Appropriate Patient: No contraindications exist and the likelihood of adverse reactions is minimal, and the drug is acceptable to the patient.

Appropriate Information: Patients should be provided with relevant, accurate, important and clear information regarding his or her condition and the medications that are prescribed.

Appropriate Monitoring: Anticipated and unexpected effects of medications should be appropriately monitored.[16] WHO advocates 12 key interventions to promote more rational use of drugs:

- Establishment of a multidisciplinary national body to coordinate policies on medicine use.
- Use of clinical guidelines.
- Development and use of national essential medicines list.
- Establishment of drug and therapeutics committees in districts and hospitals.
- Inclusion of problem-based pharmacotherapy training in undergraduate curriculum.
- Continuing in-service medical education as a licensure requirement.
- Supervision, audit and feedback.
- Use of independent information on medicines.

- Public education about medicines.
- Avoidance of perverse financial incentives.
- Use of appropriate and enforced regulation.
- Sufficient government expenditure to ensure availability of medicines and staff. [16,17]

Factor Underlying Irrational use of Drugs

There are many different factors which affect the irrational use of drugs. If one were to broadly classify the factors, they could be divided in to : those deriving from patients, chemists shop, prescribers, the workplace the supply system, industry influences, regulation, drug information and misinformation.

In each group, there can be various ways contributing to irrational use of drugs:

- **Patients** : drug misinformation, misleading beliefs, patient demands / expectations.
- **Prescribers** : lack of education and training, inappropriate role models, patient pressures, lack of objective drug information, company incentives, limited experience, misleading beliefs about drug efficacy, competition.
- **Workplace** : heavy patient load, pressure to prescribe, lack of adequate lab capacity, insufficient staffing.
- **Drug Supply System** : unreliable suppliers drug shortages, limited budgets necessitating fixed choices, expired drug supplied.
- **Chemists Shops** : patient pressures, profit motives, competition.
- **Drug Regulation** : non essential drugs available, inefficient audit system, inadequate legal implementation, and no-formal procedures.
- **Industry** : promotional activities, misleading claims, incentives. [17]

Impact of Irrational Drug Use

Irrational drug use can have various consequences, for the patient, the public, the health system and even the economy. A few important consequences are mentioned below:

- Reduction in the quality of drug therapy- this can lead to increased morbidity and mortality.
- Waste of resources- This can lead to reduced availability of other vital drugs and increased costs.
- Increased risk of unwanted effect- adverse drug reactions and the emergence of drug resistance.
- Psychosocial impacts-patients may believe that there is " a pill for every ill". [16]

National Plan to Promote Rational Drug Use

Any National Drug Policy should be concerned not only, with the supply of safe, effective and appropriate drugs for the country but also in the way that they are prescribed and dispensed by health personnel. This later aspect is often neglected as it is more difficult to address. However the impact of irrational prescribing and poor dispensing is increased morbidity and mortality, a waste of resources, unwanted side effects and adverse psychosocial reactions.

There are many factors that influence prescribing patterns, not least of which are patient demands and misbelieves. Thus the education of the patient and provision of basic health information to the public is an integral part of any Rational Drug Use Program. Interventions to improve prescribing and dispensing practices can be educational, managerial and regulatory. Their effect must be evaluated and this involves making an accurate assessment or audit of the current situation by using, for example, prescribing and dispensing indicators, knowledge, attitudes and practice studies etc. and then repeating these evaluations after the interventions have been implemented. Any program to promote Rational Drug Use requires manpower and resources which most doctors and pharmacists are expatriate trained in varying countries and institutions. Inevitably prescribing and dispensing habits vary. The studies which have been carried out to identify several undesirable trends as:-

- Polypharmacy (multiple drug prescribing).
- Patient driven prescribing.
- Over prescribing of antibiotics.
- Lack of specific standard treatment protocols leading to inconsistent prescribing resulting in the use of expensive drugs where less expensive drugs may be adequate.

- Inadequate drug information given to patients by the health care providers. This may be due to pressure of work or to language difficulties.
- Proposed Base Line Survey of Prescribing and Dispensing Indicators.
- Proposed Knowledge, Attitude and Practice Studies of Drug Use by the Public.
- ABC Analysis of Drug Expenditure.
- Proposed Review of In-service Training.
- Manpower Development.
- Resources.
- Educational Strategies to Improve Drug Use.
- Managerial Strategies to Improve Drug Use.
- Regulatory Strategies. [18]

Drug Utilization Review Board

The Omnibus Reconciliation Act of 1990 mandated that each State establish a drug use review (DUR) program by January 1, 1993. The purpose of the DUR program is to improve the quality of pharmaceutical care by ensuring that prescriptions are appropriate, medically necessary, and that they are not likely to cause adverse medical results. The Board is responsible for conducting both retrospective and prospective drug use reviews (DURs). The DUR Board also recommends and evaluates educational intervention programs.

The Board consists of eleven members: four members are pharmacists who are licensed, three members are physicians, three members are public citizens who have relevant health care experience, and two members have crossover appointments on the Pharmaceutical and Therapeutics Committee. The pharmacists are nominated by the Pharmacists Society, the physicians are nominated by the Medical Society, and the public members are nominated by the Department of Health and Social Services. Each Board member is appointed for a three year term and may be reappointed. The Secretary of the Department of Health and Social Services appoints all DUR Board members. The Board elects a Chairperson and Alternate Chairperson from among its members. The chairperson presides at all meetings of the DUR Board, which are held at least quarterly.

The DUR Board reviews predetermined standards of drug use submitted to it by the Medicaid agency or the agency's contractors. The Board evaluates the use of these standards and recommends modifications, including the elimination of existing predetermined standards or the addition of new ones. The Board makes recommendations for which combination of interventions would most effectively lead to improvement in the quality of drug therapy, and periodically re-evaluates and, if necessary, modifies the recommended interventions. The Department of Health and Social Services retains the authority to accept or reject the recommendations of the DUR Board.

All DUR Board meetings are open to the public. The DUR Board may make and enforce reasonable rules regarding the conduct of persons attending its meetings. Opportunities are provided for individuals, or citizens representing a group or groups, to appear on the agenda. Requests to appear before the DUR Board must be made in writing and received ten days before a scheduled meeting, including subject matter and speaker name for inclusion on the agenda. The ten day requirement may be waived by the Chairperson. The DUR Board will limit presentations to ten minutes, unless an extension is granted by the DUR Board.

`The official meeting schedule, agenda and minutes of DUR Board meetings can be found at the Delaware Medicaid Pharmacy webpage, which also provides access to the DUR Board's complete by laws and a list of Board members. [11]

Scope of Drug Utilization Studies

Drug utilization studies may include descriptive epidemiological approaches to the study of drug utilization, but also the assessment of how drug utilization relates to the effects of drug use, beneficial or adverse. The research in this field aims to analyze the present state and the developmental trends, of drug usage at various levels of the health care system, whether national, regional, local or institutional. Drug utilization studies may evaluate drug use at a population level, according to age, sex, social class, morbidity, among other characteristics. [19]

Conclusion

These studies are useful to provide denominators to calculate rates of reported adverse drug reactions, to monitor the utilization of drugs from therapeutic categories where particular problems can be anticipated

(e.g., narcotic analgesics, hypnotics and sedatives, and other psychotropic drugs,etc.), to monitor the effects of informational and regulatory activities (e.g., adverse events alerts, monitoring urgent safety restrictions) Drug utilization data may be used to produce crude estimates of disease prevalence (e.g., cardiovascular disease,[20] antidiabetic drugs [21]), to plan drug importation, production, and distribution, and to estimate drug expenditures.

The characterization of drug utilization may be extended linking prescription data to the reasons for the drug prescribing. They include the concept of appropriateness [22,23,24,25] that must be assessed relative to indication for treatment, concomitant diseases (that might contraindicate or interfere with chosen therapy) and the use of other drugs (interactions). Therefore they can document the extent of inappropriate prescribing of drugs (e.g. antibiotics, NSAIDs) and even the associated adverse clinical, ecological, and economic consequences [23,24,25,26] Moreover, they can also explore the percentage of drugs that adhere to the evidence-based recommendations in place for its indications.[27,13]

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ORIGINAL ARTICLE

Pattern of Adverse Drug Reaction in a Tertiary Care Hospital

Y N GOYAL, A SINGH, N B BHANSALI, C JIYO , R A MISTRY, N D JOSHI, K C SOLANKI, H K PRAJAPATI, N H DESAI, H R TRIVEDI, A SUKHLECHA.

Department of Pharmacology, M.P. Shah Medical College, Jamnagar-361008 (India)

ABSTRACT

To characterize the pattern of ADRs reported in a tertiary care hospital (Guru Gobind Singh Hospital, Jamnagar, Gujarat) over the period of six months. ADRs among indoor patients which were documented by physicians were collected daily by us. ADRs were evaluated to understand the pattern of the ADRs with respect to patient demographics, nature of the reactions, characteristics of the drugs involved. Causality, severity, preventability for the reaction were analysed. The overall incidence of ADR calculated from the patient population was 0.5%. Upon evaluation of the patient characteristics, majority of ADR were in males (59.3%). Type A reactions (73%) accounted for majority of the reports than type B (27%). Gastrointestinal system (42.1%) was the most commonly affected SOC (system organ class). Antineoplastic agents (50%) were the drug class most commonly involved. Upon causality assessment, majority of the reports were rated as probable (79.6%). Mild and moderate reactions accounted for 36% and 40%, respectively. In 5.2% of the reports, the reaction was considered to be preventable. Studies like ours enables in obtaining information on the incidence and pattern of ADRs in the local population. Such reporting programs are necessary to increase awareness about reporting of ADRs among the healthcare professionals.

Key words: Adverse Drug Reactions, Pattern of ADR, Pharmacovigilance , ADR Monitoring

Introduction

Adverse drug reactions (ADRs) are considered as one among the leading causes of morbidity and mortality. Around 6% of hospital admissions are estimated to be due to ADRs and about 6–15% of hospitalised patients experience a serious ADR.[1-3] ADR reporting has become an important component of monitoring and evaluation activities performed in hospitals.[4] Such ADR reporting programs encourage surveillance for ADRs, promote the reporting of ADRs and stimulate the education of health professionals regarding potential ADRs.[5]

Periodic evaluation of ADRs reported in a hospital helps in characterizing the pattern of ADRs and thereby help in designing steps to improve the safety of drug use in the working set up. Better health care practice could be ensured by applying this knowledge to individual patients[6]. Data generated from a hospital set up further contributes to the national and international databases on ADRs which will ultimately contribute in drug safety decisions and may serve as a basis for product-labelling revision and design patient education strategies.[7]

An attempt was made to monitor patients for Adverse Reaction in a tertiary care hospital by distributing ADR monitoring forms to physicians.

Materials and Methods

We started collecting the ADR forms from the various wards in the hospital since march 2010. This is an interim analysis of the ongoing study based on the ADR forms collected from various departments in the hospital between march 2010 to august 2010 (6 months). For the ADR collection, we used the suspected adverse drug reaction reporting forms prescribed by central drugs standard control organisation (CDSCO).

The ADR forms filled and reviewed by the physicians were collected. Data on the reported ADRs were evaluated to understand the pattern of the ADRs with respect to patient demographics, nature of the reactions, characteristics of the drugs involved. Causality, severity, preventability for the reaction were analysed.

Patient age and sex were considered for evaluation. Patients were subdivided into four age groups; children (0–12 years), young adults (13–30 years), adults (31–60 years), elderly (>60 years).

Individual reactions were classified depending on the type of reactions as type A (Augmented) and type B (Bizarre) reactions based on the classification by Rawlins and Thompson.[8]

Drugs involved in the ADRs were codified into various drug classes according to anatomical therapeutic chemical (ATC) classification based on WHO–ATC Index 2005.[9]

In order to assess the likelihood that drugs has caused the reaction, causality assessment was done using Naranjo's ADR probability scale.[10] whereby the ADRs were classified into certain, probable, possible and unlikely to be drug induced depending upon the level of association.

ADRs were categorized into preventable or not preventable using the criteria of Schumock and Thornton [11]

Depending upon the severity, ADRs were classified into mild, moderate and severe reactions using the criterion developed by Hartwig et al. for severity assessment. [4]

Results

A total of 133 ADR forms from the indoor patients were collected during these six months period. The total number of patient who were admitted was 23,069. Based on these numbers, the overall incidence of ADR from indoor patients was 0.5%. Major share of ADR were collected from the department of General Medicine, Radiotherapy and Paediatrics.

Upon evaluation of the patient characteristics majority of ADRs were in males (59.3%); Table 1. According to age, we found children (16.5%), young adults (12.5%), adults (37.5%) and old (18%); Table 1. Of the ADR collected, type A was 73% and type B 27 %;

The ADR were classified according to system organ class (SOC) and preferred terms (PT) falling under respective SOC using MedDRA 13.0 version English. The most commonly affected SOC was gastrointestinal (42%), followed by skin and subcutaneous tissue disorder (33.8%); Table 2.

Anti-neoplastic agents (50%) and anti-microbial agents (32.4%) were the drug class commonly involved; Table 3.

Upon causality assessment, majority of the reports were rated as probable (79.6%) followed by definite (13.5%); Table 4. Mild and moderate reactions accounted for 36% and 40% of the reports, respectively, and 24% of the reactions were deemed to be severe as presented in Table 4. In 5.2% of the reports the reaction was considered to be preventable as depicted in Table 4.

Discussion

ADRs can have a detrimental effect on a patients' well being and the overall health care system.[3,17] ADR collecting program in a hospital can help to assess the safety of drug therapies, measure ADR incidence rates over time, and educate health care professionals of drug effects and increase their level of awareness regarding ADRs'.[5]

In our study overall incidence of ADR amongst the indoor patients was 0.5% from the total of 23,069 patients admitted over the same duration. This was comparable to the incidence rate of 0.15% reported by Jimmy J. et al.[13] and 1.8% reported by Sriram S. et al.[14] But this incidence rate was low as compared to the results of meta analysis conducted by Lazarou et al [3], who reported an incidence of 15.1% and also by another study done by Arulmani R et al. (9.8%)[15]. The low incidence may be due to shorter duration of our study, lack of awareness amongst the physicians, and lack of spontaneous reporting culture in the hospital.

In our study most of the reactions were type A reactions (73%). But Murphy and Frigo[16] as a part of the ADR reporting program in a teaching hospital reported a higher percentage of type B reactions in comparison to type A reactions. This higher number of type A reactions may be due to the higher number of reactions reported to oncology medications, which usually are type A in nature.

Drug class most commonly involved in the reactions was antineoplastic agents; consistent with the findings of some reports [17,18], but not consistent with other studies in which antimicrobial or analgesics were most commonly associated[16,17,18,19]. Amongst the antineoplastic agents, Cisplatin was the drug most commonly associated with adverse drug events.

Gastrointestinal System (42%) was the most common affected SOC(System Organ Class) in our study and vomiting (17%) being the most common individual reaction. This was comparable to study conducted by Sriram S et al.[14] but the study done by Palanisamy S et al.[20] reported subcutaneous tissue disorder being the most common affected SOC. Antineoplastic and antimalarials were the drug class most commonly associated with the Gastrointestinal reactions. The next most common SOC affected was Skin and Subcutaneous Tissue Disorders (33.8%), with antimicrobials being the most commonly implicated drug class.

Most of the reactions belonged to the category "probable" based on causality assessment similar to the results in

Table 1: Classification* According to System Organ Class (SOC) and Preferred Terms (PT) Falling Under Respective SOC Using MedDRA 13.0 Version English.

SOC	Number of ADR reports (%) n=145	Preferred Terms (PT)	Number of ADR reports - Percentage (%)
Gastrointestinal disorder	56(42.1%)	Vomiting	23(17%)
		Diarrhoea	8(6%)
		Nausea	6(4%)
		Haemetemesis	5(3.7%)
		Gingival hypertrophy	4(3%)
		Abdominal pain	4(3%)
		Mouth ulcerations	4(3%)
Skin and subcutaneous tissue disorder	45(33.8%)	Alopecia	14(10%)
		Rash maculopapular	9(6.7%)
		Urticaria	6(4%)
		Angioedema	6(4%)
		Rash	3(2.2%)
		Fixed eruption	3(2.2%)
Blood and Lymphatic system disorder	21(15.7%)	Bone marrow failure	19(14.2%)
Nervous system disorders	17(12.7%)	Ataxia	4(3%)
Immune system disorders	5(3.7%)	Red man syndrome	4(3%)
Hepatobilliary disorders	4(3%)	Hepatitis	4(3%)
Renal and urinary disorders	4(3%)		
Ear and labyrinth disorders	3(2.2%)	Tinnitus	3(2.2%)

* SOC and PT with at least three reports are included.

Table 2 : Drug Class and Individual Drugs* Most Commonly Associated with ADRs

Drug class (according to second level of ATC classification)	Number of ADR reports (%) n=191	Drug	Number of ADR reports Percentage(%)
Antineoplastic agents (L01)	97(50%)	Cisplatin	22(11.51%)
		5 FU	13(6.8%)
		Adriamycin	11(5.7%)
		Paclitaxel	11(5.79%)
		Etoposide	10(5.2%)
		Cyclophosphamide	10(5.2%)
		Carboplatin	9(4.7%)
		Methotrexate	4(2%)
		Bleomycin	3(1.5%)
Antibacterial for systemic use(J01)	62(32.4%)	Vancomycin	12(6.2%)
		Cephalosporins	11(5.7%)
		Quinolones	5(2.6%)
		Metronidazole	4(2%)
		Amoxicillin	4(2%)
Antimalarials (PB01)	22(11.51%)	Chloroquine	13(6.8%)
		Quinine	9(4.7%)
Antimycobacterials (J04)	9(4.7%)	Isoniazid	3(1.5%)
		Pyrazinamide	2(1%)
		Rifampicin	2(1%)
		Ethambutol	2(1%)
Antithrombotic agents (B01)	3(1.5%)	Aspirin	3(1.5%)
Antinflammatory and anitrheumatic products (M01)	6(3.1%)	Paracetamol	3(1.5%)
		Diclofenac	3(1.5%)
Antiepileptic (N03)	5(2.6%)	Phenytoin	3(1.5%)
Antiemetics and antinauseants (A04)	2(1.04%)	Metoclopramide	2(1%)
Miscellaneous	4(2%)		

*Drug class and drug with at least two reports are included

Table 3: Analysis of ADRs for Causality, Severity and Preventability

Causality	Number of ADR Reports	Percentage
Definite	18	(13.5%)
Probable	106	(79.6%)
Possible	9	(6%)
Severity		
Mild	48	(36%)
Moderate	54	(40%)
Severe	32	(24%)
Preventability		
Preventable	7	(5.2%)
Not preventable	126	(94.7%)

another study [18] but different from the results observed by Murphy and Frigo [16] in which more of "possible" reactions were noticed. Considering the severity of the reactions, majority of the reactions were "moderate" in severity similar to certain other studies [21,18] but different from the results of Gonzalez-Martin et al.[22], where in more of "mild" reactions were observed. Our analysis showed that 5.2% of ADR was "preventable" which is less than that found by Kanjanarat et al. [23].

Our study has its own limitations. Firstly the duration of study was short. Lack of awareness to report ADRs combined with busy schedule of the physicians due lack of manpower in a government hospital needs to be taken into consideration while interpreting the data. But, our study data would give an insight into to the pattern of ADRs which do occur in tertiary care hospitals with a comparable pattern of patient demographics and drug usage.

In conclusion, the pattern of ADRs reported in our hospital is comparable with the results from studies conducted elsewhere in hospital set up. Results of many of the evaluated parameters were similar to other studies[17,18,19,21] while some aspects were different from other studies[16,22,23]. Difference in drug usage pattern in our set up from the settings in which the other studies were conducted could have contributed to the difference in pattern. Such studies enables in obtaining information on the incidence and pattern of ADRs in the local population. Similar reporting programs are necessary to educate and to increase awareness about reporting of ADRs among the healthcare professionals in our country.

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ORIGINAL ARTICLE

Fixed Drug Eruptions in Tertiary Care Hospital : A Study

Sanjay Kumar Kanodia[1], Anurag Tomar,[2] S R Shukla[1]

Department of Dermatology[1], Venereology & Leprosy and Pediatrics[2]
NIMS Medical College & Hospital, Nims University, Shobha Nagar, Jaipur - 303121 (India)

ABSTRACT

A two year study was conducted at National Institute of Medical Science, Jaipur. Of 65 patients clinically diagnosed as FDE (38 men and 27 women) with a mean age of 24.5 years, the duration of the disease ranged from 2 days to 5 years (mean=8.25 months). The patients ranged from13 years to 56 years of age. The lesions were solitary in 11 patients and multiple (up to 7) in rest of the patients. Eleven patients reacted to nimesulide, 4 to doxyxycline, 3 to ampicillin and acetylsalicylic acid and 2 each for Fluconazole and cotrimoxazole respectively.

Keywords: Fixed Drug Eruption (FDE), Rechallenge test, Dechallenge test

Introduction

Drug eruptions are among the common cutaneous disorders encountered by the dermatologists.[1] Fixed drug eruption (FDE), in particular, has its own characteristics and may be associated with the ingestion of a number of agents. The incidence of FDE induced by a specific drug depends on the frequency of the agent used in a given part of the world.[2] Fixed drug eruption (FDE) appears as an oval, erythematous patch and recurs at the same areas following every administration of the responsible drug. Limbs and trunk are most commonly affected, but involvement of glans penis and lips is not uncommon.[3,4]

Cell mediated immunity is thought to play the major role in the development of lesions in this condition. CD8+ cytotoxic T cells persist within lesional skin and contribute to immunological memory.[5] Intraepidermal CD8+ memory T cells are greatly enriched in resting lesional skin of fixed drug eruption; upon activation, they can rapidly produce IFN-Y, transiently acquire a natural killer phenotype, and express cytotoxic granules, followed by localized epidermal injury.[6]

The drugs causing fixed drug eruptions are sulphonamides, barbiturates and NSAIDs including aspirin, oxyphenbutazones, phenazones, paracetamol, nimesulide and ibuprofen.[7] In the studies conducted previously antimicrobials including sulphonamides are implicated to be the most common agents causing fixed drug eruptions.[7] In the post millennium era, almost everyday a new drug enters market, therefore, a chance of a new drug reaction manifesting somewhere in some form in any corner of world is unknown or unreported. With the availability of NSAIDs as over the counter drug in India, the chances of drug reactions have also increased proportionately. Although a large number of drugs have been incriminated to cause FDE, certain drugs are more often responsible for causing the same. This study aims to show the agents commonly causing the FDE in post millennium era in a tertiary care hospital.

Materials and Methods

The study was done at National Institute of Medical Sciences and research, Jaipur from January 2008 to March 2010. Twenty five patients with the clinical diagnosis of FDE were enrolled and interrogated regarding the onset, duration and drugs taken for any specific complaints. Rechallenge test was done for the suspected agent with a quarter of a single therapeutic dose, followed if necessary by a step-wise increase to one half, one full dose and the double of a dose. Provocation was considered negative if exacerbation of the lesion was not seen within 24 hours even after the double dose. Erythema, itching and burning around the existing lesion were taken to indicate a positive provocation test. The drugs used for provocation include nimesulide, ampicillin, doxycycline, fluconazole, cotrimoxazole and aspirin.

Results

There were 65 patients (38 males and 27females) from 13 years to 56 years with a mean age of 24.5 years. Table 1 shows that the patients presented as early as 2 days to upto

5 years of period (mean=8.25 months). The lesions were solitary in 11 patients to up to 7 in rest of the patients. The maximum number of patients had lesion on genitals and on upper extremity. Hyperpigmented macular lesions were present in 52 patients along with erosive, maculoerosive and bullous lesion in 24, 17 and 7 patients respectively.

The suspected offending drug was withdrawn in all patients. Further progress of lesions stopped in all and in 40 patients reduction of intensity of lesions started. Rechallenge was attempted with the offending drug administered in 1/4th of the dose the patient was taking. This resulted in reappearance / enhancement in the intensity of lesion in four patients- one each with nimesulide, doxycycline and one erach with acetyl salicylic acid and cotrimoxazole respectively.

Out of 65 cases, the rechallenge test was positive in se of drugs as shown in table 2. Nimesulide was most common offending agent affecting 11 patients followed by 4 in doxycycline, 3 each in ampicillin and acetylsalicylic acid and 2 each to Fluconazole and cotrimoxazole respectively (table 2). All other 40 cases where the rechallenge was negative, the dechallenge was done which showed favorable result in form of subsidence of further progress of lesion as soon as the drugs were withdrawn.

Discussion

Drugs causing fixed drug eruptions differ from one region to the other depending on the pattern of morbidity, range and availability of drugs, prescribing habits of the medical practitioners, socioeconomic status of the community, and the adherence to drug control measures.[5] It is no longer

Table 1 Characteristic Features Patients with Fixed Drug Eruptions

Characteristics	Variables
Sex	Male=38 Female=27
Age	Mean age=24.5 years Range= 13-56 years
Onset of disease	Range =18 hr- 3 days Mean= 1.5 days
Duration of disease	Range =2days -5 years Mean time=8.25 months
Number of lesion	Range=1-7 Mean=3.5
Site of lesions	Oral mucosa= 15 Upper extremities=32 Trunk =17 Genitalia=32 Lower extremities=23 Buttock =4 *(11 patients had single lesion while Rest of the patients had multiple lesions)
Type of lesion	Hyperpimented Macule=52 Erosive=24 Macule +Erosive=17 Bullous=4

Table 2 Rechallenge and Dechallenge Test with Suspected Drugs in P atients with Fixed Drug Eruptions

Suspected Drugs	Positive Rechallenge test				Positive Dechallenge test (subsidence of lesion after withdrawal of the suspected drug)
	¼ Drug dose	½ Drug dose	1 Drug dose	Total (n=25)	
Nimesulide	1	3	7	11	14
Doxycycline	1	2	1	4	7
Ampicilline	-	1	2	3	3
Acetyl salicylic acid	1	2	-	3	6
Fluconazole	-	1	1	2	2
Cotrimoxazole	1	1	-	2	8
Total	4	10	11	25	40

possible to prepare a list of common causes of drug eruptions that would remain valid for more than a few years. Studying the causative agents of a drug eruption is therefore worthwhile from time to time.

Observations in the present study implicate nimesulide as the most common agent causing FDE, which differs from other studies. In the earlier studies the antimicrobials are most commonly implicated for FDEs, with cotrimoxazole on the top of the list in the two series.[9, 10] In the context of pain killers also acetyl salicylic acid and phenylbutazone are the most common offending agents.[11] The quantitative difference in the actions of different NSAIDS may be explained by the differences in the sensitivities of COX (PG synthetase) in different tissues. The cyclo-oxygenase in the brain is much more sensitive to parcetamol than cyclo-oygenase in the blood vessels. Many NSAIDs non-selectively inhibits COX-1 and CoX-2, while piroxicam and indomethacin are 10-40 fold selective for COX-1 whereas nambutone is 15 fold selective for COX-2. For nimesulide the ratio of activity against COX-2 and COX-1 is 5-16.[12]

The more and more use of nimesulide and availability as over the counter drug in Indian market could be one of the reasons for more occurrences of adverse events to the drug- nimesulide. The underreporting of the side effect of nimesulide in the western world may be possibly that due to non-availability of nimesulide in the western world.

Fixed drug eruptions form the important clinical entity in dermatology practice. When the drugs are marketed and used extensively the adverse events are also not uncommon. As the newer drugs are being introduced in the market, the pattern of drug reaction is also changing as is evident from the present study. Though there are limitations in the spontaneous reporting of adverse drug reactions, but it has proved to be an effective tool in Pharmacovigilance. Our study aims heading towards the same system.

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ORIGINAL ARTICLE

A Retrospective Descriptive Study of Drug Utilization and ADR Monitoring in Mania and Bipolar Affective Disorder in the Psychiatric Unit of a Teaching Hospital

KINGSHUK LAHON, HARSHA M SHETTY, AMITH PARAMEL, GYANESHWAR SHARMA

Department of Pharmacology, Mahatma Gandhi Medical College and Research Institute (MGMCRI) Pondicherry - 605001 (India)

ABSTRACT

Discrepancies between clinical trials and actual utilization may reveal drug use associated with lower efficacy or increased adverse effects. There have been recent changes in prescribing patterns in mania and bipolar affective disorder (BPAD). Adverse drug reactions (ADRs) of psychotropic drugs are detectable and often preventable. Hence, we wanted to study drug utilization and ADR monitoring in mania and BPAD in the psychiatric unit of a teaching hospital. Our objectives were to observe the prescribing pattern in mania and BPAD, assess the rationality of the prescriptions and detect ADRs. Retrospective observational study of case records of patients diagnosed with mania or BPAD in the psychiatric unit of a teaching hospital during the period 1st January 2006 to 31st December 2006. Total number of prescriptions was 31 and 57 drugs were prescribed. Of them, 35 (61.40%) were mood stabilizers, 14 (25%) sedative hypnotics, 7 (12.50%) antidepressants and 1 (1.75%) was propranolol. Average number of drugs per prescription - 1.84, drugs prescribed by generic name - 82.46%, no FDCs or injections, prescribing from WHO EML – 40.35%. ADRs detected were tremors (valproic acid), drug-induced mania (duloxetine), weight gain (valproic acid + olanzapine) and amnesia (valproic acid + olanzapine + clonazepam). Mood stabilizers were the most common drugs prescribed for mania and BPAD. Valproic acid was the most common mood stabilizer, lorazepam, the most common sedative hypnotic and duloxetine, the most common antidepressant prescribed. Polypharmacy was absent and as per WHO prescribing indicators, favourable outcomes were seen for 4 indicators, and unfavourable for 1. Most common ADR seen with mood stabilizers was weight gain due to valproic acid and olanzapine.

KEY WORDS: Drug Utilization, Mania, Bipolar Affective Disorder (BPAD), ADR Monitoring

Introduction

Pharmacoepidemiological studies seek to assess the utilisation and impact (benefit and risk in 'real life' conditions) of healthcare products at the level of the population actually treated, not just on the limited target population in clinical trials.[1] Discrepancies between clinical trials and utilization in naturalistic conditions may reveal drug use associated with lower efficacy or with increased risk of adverse effects. They should be identified to monitor, evaluate and modify, if necessary, the prescribing habits of practitioners to maintain standards of medical treatment and make medical care more rational and cost effective.

The gap between guidelines and utilisation is well established for psychotropic medications. Lithium carbonate has long been the gold standard among mood stabilizers for treatment of mania and prophylaxis of Bipolar Affective disorders (BPAD). Of late, the limitations and adverse effects of lithium salts have driven researchers to look for alternatives, resulting in the discovery of mood stabilizing properties of anticonvulsants and antipsychotics. This has led to changes in prescribing patterns in mania and BPAD.

Adverse drug reactions (ADRs) are a major cause of morbidity and mortality, with around 6% of hospital admissions estimated to be due to ADRs.[2] Psychotropic drugs are associated with ADRs which can be detected and often, prevented.

Hence, we wanted to study drug utilization and ADR monitoring in mania and BPAD in the psychiatric unit of a teaching hospital in Pondicherry. Our objectives were:

1. To observe the prescribing pattern in mania and BPAD among psychiatrists in our hospital
2. To assess the rationality of the prescriptions
3. To detect ADRs of psychotropic drugs

Methods

We conducted a retrospective observational study of case records of patients diagnosed with mania or bipolar affective disorder as per ICD-10[1] criteria in the psychiatric unit of a teaching hospital in Pondicherry during the period 1st January 2006 to 31st December 2006. Data were entered in a pre-designed proforma. (Fig1)

From the multiple prescriptions in the case record with follow-up visits, we took all prescriptions containing at least one mood stabiliser or antidepressant (drugs used for definitive therapy in mania and BPAD) as one prescription. Substitution or addition of another mood stabiliser or antidepressant to the existing regimen was regarded as a separate prescription. However, prescriptions which were not given in the department of Psychiatry, and containing drugs for non-psychiatric co-morbid conditions were excluded.

The documented data were subjected to analysis for the following parameters:

1. Demographic details (Gender and age distribution)
2. Distribution of mania and BPAD
3. Psychotropic drugs prescribed and prescribing pattern
4. Rationality of prescription according to WHO prescribing indicators.
5. Adverse drug reactions (ADRs) of psychotropic drugs

ADRs were detected on the basis of causality analysis of documented adverse events using Naranjo's scale.[4]

Descriptive statistical tools were used for analysis.

As it was a non-interventional study, the institutional research committee granted waiver on the assurance that subject confidentiality would be maintained.

Results

Gender and Age distribution: There were 20 patients of mania or BPAD, of which 12 were males and 8 were females. Age distribution is shown in Table 1.

Distribution of Mania and BPAD: There were 3 patients diagnosed with mania (15%) and 17 with BPAD (85%).

Psychotropic Drugs Prescribed and Prescribing Pattern: Total number of prescriptions was 31 and 57

Table 1: Age Distribution of Patients with Mania and BPAD

Age range (years)	No of patients (n=20)	Percentage (%)
1 - 10	Nil	0
11 - 20	3	15%
21 - 30	5	25%
31 - 40	7	35%
41 - 50	3	15%
51 - 60	Nil	0
61 - 70	1	5%
71 – 80	Nil	0
>80	1	5%

drugs were prescribed (Table 2). Of them, 35 (61.40%) were mood stabilizers.

In BPAD, valproic acid was prescribed on 16 occasions, olanzapine on 9 occasions, lithium and risperidone on 2 occasions each and haloperidol on 1. In mania, valproic acid was prescribed on 3 occasions and olanzapine on 1.

existing regimen on 3 occasions. Risperidone was later added to olanzapine on 2 occasions and olanzapine added to valproic acid on 1 occasion. No substitution or addition of antidepressant was seen.

Rationality of Prescriptions: The number of drugs per prescription are as follows – 1 per prescription on 6

Table 2: Prescribing Frequency of Psychotropic Drugs in Mania and BPAD

Psychotropic drug	No of times prescribed (n=57)	Percentage (%)
Valproic acid	20	35.08
Olanzapine	10	17.54
Lithium	2	3.51
Risperidone	2	3.51
Haloperidol	1	1.75
Lorazepam	7	12.28
Clonazepam	4	7.02
Zolpidem	3	5.26
Duloxetine	5	8.77
Escitalopram	1	1.75
Mirtazapine	1	1.75
Propranolol	1	1.75

Sedative hypnotics were prescribed on 14 occasions (25%), antidepressants on 7 (12.50%) and propranolol on 1 occasion (1.79%).

Substitution and Addition of Mood Stabilizer or Antidepressant: Change of mood stabiliser was required on 9 occasions. Lithium, prescribed outside our hospital was substituted in 2 patients of BPAD and replaced by valproic acid. Olanzapine was replaced by valproic acid on 3 occasions, valproic acid was replaced by olanzapine on 2 occasions, risperidone by olanzapine and haloperidol by valproic acid on 1 occasion each.

We observed addition of another mood stabilizer to an

occasions (19.35%), 2 on 15 occasions (48.38%), 3 on 8 (25.81%) and 4 on 2 (6.45%) occasions. More than 4 drugs were not prescribed to any patient.

As per WHO Prescribing indicators, we observed:

- Average number of drugs per prescription: 1.84 (57/31)
- Percentage of drugs prescribed by generic name: 82.46% (47/57 X 100)
- Percentage of Fixed dose combinations of drugs: Nil

- Percentage of encounters for prescribing injections: Nil
- Percentage of drugs prescribed from WHO Essential Medicines List (EML): 40.35%
- Percentage of drugs prescribed from National List of Essential Medicines (NLEM, endorsed 2002) was 75.44%.

ADRs and Causality Analysis: Adverse events recorded in the case sheets were antidepressant (duloxetine) - induced mania, tremors caused by valproic acid, 2 cases of weight gain on concurrent treatment with olanzapine and valproic acid and 1 case of amnesia on concomitant treatment with olanzapine, valproic acid and clonazepam. Duloxetine - induced mania was reversed on stopping of the antidepressant and tremors caused by valproic acid were treated with administration of propranolol. On applying Naranjo's scale, we could assign a score of 5 to drug induced mania and tremors. For weight gain and amnesia, we could give a score of 3.

Discussion

Gender and Age distribution: Mania and BPAD occurred more in males (60%) than females (40%). No significant sex differences have been found in the rates of bipolar disorder and mania in some previous studies[5] although others have found differences with male dominance in one study[6] and female in another[7].

Age distribution shows 3 patients below 18 years, 15 patients in the 18 - 64 year age group and 2 patients above 65 years. 12 patients (60%) were aged between 21- 40 years.

Age distribution shows maximum prevalence of mania and BPAD in adults (75%), followed by paediatric (15%) and elderly (10%) age groups. Most patients (60%) were in the 21 – 40 year age group, compared to studies where in patients were in the 18 - 27 years age group[8].

Psychotropic Drugs Prescribed and Prescribing Pattern: Most common drugs prescribed were mood stabilizers (61.40%), followed by sedative hypnotics, antidepressants and propranolol. In other studies, antidepressants were the most prescribed agents especially in bipolar disorders[6,7]. Most common mood stabiliser prescribed was valproic acid (35.08%), followed by olanzapine, risperidone, lithium and haloperidol. Earlier, lithium was foremost among mood stabilizers prescribed,[6] but now it has been replaced by valproic acid in more recent studies[7]. Use of atypical antipsychotics and concomitant sedative-hypnotics/anxiolytics also follows western trends.[6,7]

A single mood stabilizer at a time was used (prevalence of 80%) in all except 3 patients of BPAD and 1 patient of manic episode, in which 2 drug regimen (olanzapine and valproic acid) was started immediately on diagnoses.

Substitution and Addition of Mood Stabilizer or Antidepressant: Substitutions of mood stabilizers did not follow any particular pattern, but 2 patients on lithium therapy were tapered off and substituted by valproic acid due to lack of therapeutic drug monitoring facilities in the department. Lack of or decreased clinical benefit was the other reason for change of mood stabilizers.

Most common adjunctive mood stabilizer was risperidone (66.66%) followed by olanzapine. Most common sedative hypnotic/anxiolytic prescribed was lorazepam (50%), followed by clonazepam and zolpidem.

Most common antidepressant prescribed was duloxetine (71.43%), followed by escitalopram and mirtazapine.

Rationality of Prescriptions: There was no poly-pharmacy according to the most popular definitions of poly-pharmacy, that is, there was no prescribing of psychotropic drugs which did not match diagnosis and there was no prescription with more than 6 drugs.[9]

The average number of drugs per prescription was less than 2, which is recommended. Prescribing by generic names was high (82.46%). There were no fixed dose combinations (FDCs) or injectible preparations prescribed, which indicate rational prescribing practices. The percentage of drugs prescribed from the 16th WHO Essential Medicines List was low. The percentage of prescribing from the National Essential Medicines List (endorsed 2002) was higher (75.44%). This difference was due to the presence of atypical antipsychotics and sedative hypnotics - lorazepam and zolpidem in the NLEM compared to the WHO EML.

ADRs and Causality Analysis: All the ADRs detected were of known types.[10] Weight gain was the most common ADR observed in the prescriptions, with both olanzapine and valproic acid as possible causative agents. We assigned possible causality to the case of amnesia on concomitant treatment with olanzapine, valproic acid and clonazepam also. However, we could assign probable causality to the ADRs – drug induced mania and tremors.

Limitations of the Study are small sample size, lack of patient care indicators and some facility indicators which

can be derived prospectively. For causality assessment of ADRs, we could not assign causality beyond a probable score for the ADRs. It was not possible to monitor actual use or compliance with prescribed medication.

Strengths of the Study are the use of a structured proforma for data collection with details of drug prescriptions on follow up visits. ADR monitoring data can increase alertness among psychiatrists to the most common ADRs of the mood stabilizers in the study population and also detect signals if present.

Conclusion: Our study shows that mood stabilizers were the most common drugs prescribed for mania and BPAD. Valproic acid (35.08%) was the most common mood stabilizer, lorazepam, the most common sedative hypnotic and duloxetine, the most common antidepressant prescribed. Polypharmacy was absent. As per WHO prescribing indicators for rational use, favourable outcomes were seen for 4 indicators, and unfavourable for 1. Most common ADR seen with mood stabilizers was weight gain due to valproic acid and olanzapine.

Recommendations: Prescribers should be encouraged to restrict prescribing of sedative hypnotics and record patients' compliance with the prescribed medications. Monitoring of weight at baseline and during therapy with valproic acid can detect and prevent or control the weight gain among patients. Mania induced by antidepressant therapy can also be prevented by careful dose titrations and monitoring of the patient. Such measures will promote rational use of medicines and patient compliance and improve healthcare.

Acknowledgment

Staff of Medical records and Print sections of Mahatma Gandhi Medical College and Research Institute, Pondicherry - 607402

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ORIGINAL ARTICLE

High Dose vs Low Dose Oxytocin for Labour Augmentation: A Partographic Analysis

APARNA SHARMA

Department of Obstetrics and Gynaecology
Mahila Chikitsalaya, SMS Medical College, Jaipur-302001 (India)

ABSTRACT

This study was randomised trial to compare labour outcomes using high dose oxytocin or low dose oxytocin management protocols. Healthy nulliparous women in active labour, at term, with a healthy singleton pregnancy and cephalic presentation were enrolled. The women were randomised to either high dose oxytocin (n=100) or low dose oxytocin (n=100) management protocols. Both the groups used entailed using a single line partogram, a vaginal examination every two hours and use of an oxytocin infusion if the line was crossed. The study contrasted two interventions for labour augmentation: high-dose vs low-dose oxytocin. For the women assigned to high dose oxytocin (n=100), the cesarean-section rate was 10.1 per cent, as compared with 14 per cent for those assigned to traditional management (p=0.18). The 26 percent reduction in the cesarean-section rate was due primarily to a decrease in dystocia. After we controlled for potential confounding variables, the reduction in the rate of delivery by cesarean section was statistically significant (odds ratio for women given active as compared with traditional management, 0.57; 95 per cent confidence interval 0.36 to 0.95). The program we studied for the active management of labor with high dose oxytocin reduces the incidence of dystocia and increases the rate of vaginal delivery without increasing maternal or neonatal morbidity.

Key word : Oxytocin, Partographic Analysis

Introduction

The rise in cesarean section continues to be a matter of obstetric concern.[1] Recent reports suggest that high cesarean rates may have an adverse impact on maternal and neonatal morbidity and mortality.[2] Dystocia is the leading indication for primary cesarean section.[3-4] Inadequate uterine activity has been described as the most frequent cause of dystocia.

Augmentation of labor with oxytocin is a frequent intervention in modern obstetric practice.[5] When labor fails to progress, oxytocin is administered to augment contractile effort and to correct dystocia with the objective on achieving a normal vaginal delivery.[6] Oxytocin has been demonstrated to increase the frequency and intensity of uterine contractions when spontaneous uterine contraction is inadequate and the progress of labour is slow. Oxytocin protocols can be categorized as high dose or low dose protocols depending on the initial dose and the amount and rate of sequential increases in dose. Despite the frequency with which oxytocin is used in clinical practice, there is little consensus regarding the optimal dose of oxytocin for labour augmentation.[7]

Over the last two decades, a number of randomized clinical trials have assessed the relative effectiveness of different oxytocin protocols for the treatment of dystocia, including varying dose regimens. This study was designed to estimate the efficacy and safety of high dose vs low dose oxytocin in the augmentation of labour on method of delivery and on indicators of maternal and neonatal morbidity.

Dujardin et al.[8] have shown there is a significant increase in the need for neonatal resuscitation once the alert line is crossed and a significant increase in perinatal mortality if the action line is crossed.

Thornton and Lilford[9] using meta-analysis have shown that there is no convincing evidence that the early use of oxytocin in slow progress of labour confers any advantage to the mother or baby. Hence, there is considerable doubt as to which protocol is best for management of labour. To resolve this dilemma, a randomised trial was conducted on

nulliparous women in labour to compare a policy of high dose oxytocin management with low dose oxytocin management as recommended by the WHO.

Materials and Methods

Nulliparous women with term pregnancy in the active phase of labour without exclusion criteria were invited to participate in the trial. The active phase of labour was identified when contractions were regular and painful, and the cervix was four or more centimeters dilated. Exclusion criteria were obstructed labour, non-cephalic presentation, fetal distress on admission, severe maternal disease.

The doctors working in the labour ward of centre were responsible for recruitment and consent. The protocol used was determined by taking the next sealed opaque study envelope from a box in the labour ward. Each envelope contained the detailed protocol. Randomisation was based on a computer-generated list of random numbers.

Both the groups were managed using a partogram with a single alert line. The cervical dilatation was plotted on the alert line and a repeat vaginal examination was performed after two hours. If cervical dilation had progressed on or to the left (above) the alert line, the cervix was re-evaluated in two to four hours depending upon when full cervical dilation was anticipated. If cervical dilation had moved to the right of the alert line, the managing clinician was asked to confirm fetal wellbeing and exclude gross cephalopelvic disproportion. As long as neither condition was present, the clinician started an oxytocin infusion according to the standard labour ward protocol to ensure adequate contractions. The protocol requested that intact membranes be ruptured at this stage. Reassessment was to occur after two hours. If obstructed labour or fetal distress was diagnosed, a cesarean section was performed. If progress was good, the woman was reassessed every two hours until delivery. Analgesia was prescribed according to request.

The study contrasted two interventions for labour augmentation: high-dose vs low-dose oxytocin. "High dose" was defined as an initial dose of ≥ 4 mU/min and dose increments of at least 4 mU/min; "low-dose" protocols were defined as those with an initial dose ranging between 1-4 mU/min with increments of 1-2 mU/min.

The attending physician made the diagnosis of cephalopelvic disproportion when there were three pluses of moulding of the fetal skull and poor cervical dilation. Where there were no signs of severe moulding, the indication for cesarean section was recorded as poor progress. The diagnosis of fetal distress was made when recurrent late decelerations on continuous electronic fetal heart rate monitoring was present.

The key end points for the study were the duration of active phase of labour, number of women requiring operative delivery (vaginally or abdominally) and neonatal morbidity or mortality.

Informed written consent was obtained from each woman in the labour ward before entry to the study. The Ethics Committee of the S.M.S. Medical College, Jaipur approved the study.

Results

This study was conducted between June, 2010 to March, 2011. A total of 200 nulliparous women were recruited and randomised to the study. 100 women were in the high dose oxytocin management group and 100 in the low dose oxytocin management group.

Demographic data are presented in Table 1. In addition to the variables listed, there were no significant differences between the two groups in the incidence of prenatal obstetrical or medical complications, height or weight before pregnancy, or total weight gain during pregnancy.

Those in the high dose oxytocin group did not require augmentation of labor with oxytocin or conduction anesthesia any more frequently than the expectant group of patients. For women in the high dose oxytocin group who required augmentation, however, the maximal rate of infusion of oxytocin was significantly higher than in the low dose oxytocin group.

There was a 26 percent reduction in the overall rate of cesarean section in the high dose oxytocin group 11 percent, as compared with 14 percent in the expectant group; $p=0.18$ (Table 2). The reduction was due primarily to a decrease in the frequency of arrest disorders. After we controlled for potential confounding variables (maternal age, height, weight before pregnancy, weight gain during pregnancy, gestational age, infant's birth weight, degree of dilation, effacement, and membrane status on admission), the reduction in the rate of cesarean delivery delivery was statistically significant ($p<0.05$; odds ratio, 0.57; 95 percent confidence interval, 0.36 to 0.95). The rates of operative vaginal delivery did not differ significantly

Table 1. : Characteristics of Labor in the Study Groups

Characteristics	High Dose Oxytocin (N=100)	Low Dose Oxytocin (N=100)	P Value
Maternal age (yr)	27.3±5.8	26.7±6.1	NS
Gestational age (wk)	39.8±1.1	39.7±1.1	NS
Dilation at admission (cm)	3.2±1.5	3.2±1.5	NS
Maximal dose of oxytocin (mU/min.)	17.3±9.4	10.8±6.7	<0.0001

* Values are mean ± SD. NS denotes not significant.

between the high dose oxytocin and low dose oxytocin groups.

Table 3 summarizes the progress of labor in patients who delivered vaginally. The interval from admission to amniotomy was significantly shorter for patients in the high dose oxytocin group, and therefore the degree of cervical dilation at the time of membrane rupture was lower (3.9 cm vs. 4.6 cm, $p< 0.001$). Both the first stage of labor and the total duration of labor were significantly shorter for patients whose labor was actively managed; earlier amniotomy, earlier use of oxytocin, and a more rapid response to augmentation also, appeared to contribute to this reduction

As shown in Table 4, were were no increases in complications of labor associated with high dose oxytocin. In fact, aggressive management was associated with reduction in maternal infectious morbidity (choriomnionitis and endometritis). The rate of infusion of oxytocin was lowered or the infusion was stopped altogether less frequently for patients in the aggressive management group than for low dose oxytocin patients. Despite the relatively large number of patients in each group who required a decrease in the oxytocin infusion rate, few operative interventions were necessary because of abnormalities in the fetal heart rate.

No significant differences or any other reason in neonatal outcome were detected between the high dose oxytocin and low dose oxytocin groups. No statistical or clinical differences were observed in any of these measures after th

Table 2 : Type of Delivery According to Study Group.

Type of Delivery	High dose Oxytocin (N=100)	Low dose Oxytocin (N=100)
Cesarean section – no. (%)	11	14
FHR abnormalities	1	1
Arrest of dilation	8	10
Arrest of descent	2	3
Vaginal delivery – no. (%)	89	86
Spontaneous	80	78
Outlet, low forceps	2	3
Vacuum	7	5

* FHR denotes fetal heart rate. $p<0.05$ for the comparison of the rate of cesarean section in the two groups, by logistic regression.

Table 3. : Labor Intervals for Patients with Vaginal Deliveries, According to Study Group.

Interval	High dose Oxytocin (N=100)	Low dose Oxytocin (N=100)	P Value
Admission to amniotomy	0.55±0.23	2.36±2.21	<.001
Amniotomy to delivery	5.63±2.56	5.79±3.23	NS
Admission to augmentation	2.73±1.91	4.11±2.26	<0.0001
Augmentation to 10-cm dilation	3.16±2.19	4.13±2.57	<0.0001
Augmentation to delivery	4.62±2.90	5.37±3.12	<0.02
Length of first stage	5.05±2.33	6.72±3.64	<0.0001
Length of second stage	1.44±.097	1.43±1.08	NS
Admission to delivery	6.49±2.75	8.15±3.89	<0.0001

* Plus – minus values are means ± SD. NS denotes not significant.

we controlled for the use of oxytocin type of delivery, and the indication for operative delivery. Examination of the newborns, both at delivery and at discharge, did not detect any increase in morbidity (e.g., fractures,cephalhematomas, or hyperbifirubinemia) in the infants of mothers whose labor was actively managed.

Discussion

In this prospective, randomized trial, the active management of labor with high dose oxytocin was associated with a statistically significant decrease in the rate of cesarean section with no detectable increase in maternal or fetal morbidity. This reduction was primarily due to a decrease in the frequency of dystocia. The criteria for the diagnosis of labor used in the active management of labor may also contribute to the efficacy of the program.

Among the patients who delivered vaginally, amnitomy was performed earlier in the with high dose oxytocin group, but the interval from amniotomy to delivery was similar in both groups. Both early amniotomy and the early diagnosis and treatment of dysfunctional labor therefore appear to be important in shortening labor.

Table 4. : Complications of Labor and Delivery, According to Study Group.

Complications	High dose Oxytocin (N=100)	Low dose Oxytocin (N=100)	P Value
Antepartum meconium	8	11	NS
Placental abruption	0	0	NS
Oxytocin decreased or stopped	46	57	<0.05
Choriomnionitis	5	10	<0.01
Endometritis	2	3	NS

* Plus – minus values are means ± SD. NS denotes not significant.

This suggests that the efficacy of active management is not due solely to the higher doses of oxytocin used, but rather to the program of labor management as a whole.

Discussion

In this prospective, randomized trial, the active management of labor with high dose oxytocin was associated with a statistically significant decrease in the rate of cesarean section with no detectable increase in maternal or fetal morbidity. This reduction was primarily due to a decrease in the frequency of dystocia. The criteria for the diagnosis of labor used in the active management of labor may also contribute to the efficacy of the program.

Among the patients who delivered vaginally, amnitomy was performed earlier in the with high dose oxytocin group, but the interval from amniotomy to delivery was similar in both groups. Among the patients who received oxytocin and delivered vaginally, those in the with high dose oxytocin group had a shorter interval from the diagnosis of labor to the beginning of the oxytocin infusion and a significantly but less dramatically shorter interval from the initiation of augmentation to delivery. Both early amniotomy and the early diagnosis and treatment of dysfunctional labor therefore appear to be important in shortening labor. This suggests that the efficacy of active management is not due solely to the higher doses of oxytocin used, but rather to the program of labor management as a whole.

A frequent challenge for obstetricians is how to reduce maternal and neonatal morbidity when faced with arrested or protracted progress in labor. Although oxytocin is widely used in obstetric care, there is a lack of consensus with respect to the optimal oxytocin dosage, safety, and efficacy of this intervention. Relative to vaginal delivery, cesarean section has been shown to be associated with a range of serious maternal and neonatal morbidities. The rate of cesarean delivery has been shown to be associated with the need for postpartum antibiotic treatment and an increased risk of disorders of placentation and unexplained stillbirths in subsequent pregnancies.

In summary, high dose oxytocin augmentation of labor was found to be associated with a moderate reduction in the rate of cesarean section and a small increase in the rate of spontaneous vaginal deliveries and shortened labor.

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J Pharmcovig Drug Safety 2011 (January-March) Volume : 8 Issue : 1 (Page 39-42) SHORT COMMUNICATION

Spontaneous Reporting as a Future of Safe Drugs

MAHVASH IRAM, R H SHOBHA RANI

Department of Pharmacy Practice,
A1, Ameen College of Pharmacy, Bangalore-560027 (India)

ABSTRACT

Spontaneous reporting is undoubtedly the most cost effective approach for the post-marketing identification of new adverse drug reactions (ADRs). Computerized databases will work only for prescription drugs; adverse events involving over-the-counter medications will be overlooked. Several time even long-established over-the-counter products have been found to cause side effects serious enough to be pulled from the market. A system of spontaneous reporting may be more effective at picking up these problems. Continuous monitoring of the side effects, contraindications and outright harmful effects of drugs which can result in a high degree of morbidity and in some cases, even mortality, is essential to maximise benefits and minimise risks

Key words: Spontaneous Reports, Adverse Drug Reactions, Signaling, Health Care Professionals.

Introduction

Spontaneous reporting is the core data-generating system of international Pharmacovigilance, relying on healthcare professionals to identify and report any suspected adverse drug reaction to their national Pharmacovigilance centre or to the manufacturer. Spontaneous reports are almost always submitted voluntarily.[1] These are a crucial element in the worldwide enterprise of Pharmacovigilance and form the core of the World Health Organization Database, which includes around 3.7 million reports (September 2006), growing annually by about 250,000.[1]

Spontaneous case reports of adverse events submitted to the sponsor and FDA, generates signals of adverse effects of drugs. The quality of the reports is critical for appropriate causality assessment between the product and adverse events.[2] FDA recommends that sponsors make a reasonable attempt to obtain complete information for case assessment during initial contacts and subsequent follow-up, especially for serious events, and encourages sponsors to use trained health care practitioners to query reporters. FDA suggests that sponsors initially evaluate a signal generated from post marketing spontaneous reports through a careful review of the cases.[3]

The prime focus of spontaneous reporting system is to detect serious unknown adverse reactions (ADR's). All reports of ADR's are reviewed and analysed to generate signals or warnings of serious yet unrecognised drug associated events that indicates a public health problem.[4]

Reporting System and Drugs

The term spontaneous refers to "voluntary anecdotal" reports from providers regarding individual patients; these reports do not arise from formal studies or case reports in literature[4]. The collection of these reports has become the foundation of Post Marketing Surveillance programs largely because of the high volume of information they supply, low maintenance costs and their demonstrated usefulness when supervised by experienced evaluators.[5]

Continuous monitoring of the side effects, contraindications and outright harmful effects of drugs which can result in a high degree of morbidity and in some cases, even mortality, is essential to maximise benefits and minimise risks. No degree of care and caution at the pre-clinical and clinical testing stages can guarantee absolute safety, when a drug is marketed and prescribed to large populations across the Country and outside.[6]

A number of studies conducted through out the world have demonstrated that ADR's significantly decrease the quality of life, increase hospitalisations, prolong hospital stay and

increase mortality. A study by Vikas Dhikav et.al; described ADR's to be the 4th largest cause of death and it was found that 3.2 out of every 1,000 hospitalized patients die each year as the result of adverse reactions to prescription drugs.[7]

With more new medicines being approved for marketing more quickly without long term safety studies by regulatory authorities and switching of prescription only medicines (POM) to over the counter medicines (OTC) to be used more widely by patients for self -medication, the general public is at risk of exposing itself to ADRs.In India, general practitioners, with an large outpatient base tend to be among the first ones to use the drugs entering the market, hence they are in the best position to assess the adverse drug reactions associated with drugs.[8]

In India, The National Pharmacovigilance Advisory Committee (NPAC) monitors the performance of various centers & performs the functions of —Review Committe for Pahramcovigilance program. The NPAC also recommends possible regulatory measures based on data received from various centers. The Central Drugs Standard Control Organization (CDSCO) is initiating a countrywide Pharmacovigilance program under the aegis Government of India.[9] The program has a three-tier structure consisting of peripheral, regional and zonal Pharmacovigilance Centers in addition to the National Pharmacovigilance Advisory Committee and the National Pharmacovigilance Center based at the Central Drugs Standard Control Organization, New Delhi at its apex. All centers are suppose do report alarming or critical adverse drug reactions to the National Pharmacovigilance Center directly so that regulatory decisions can be taken promptly.[10]

Systematic recording of health care treatment associated adverse events was first proposed by Finney after the Thalidomide tragedy. A large body of post thalidomide safety experience suggests that the spontaneous reporting programs can contribute to a better understanding of the risk-benefit ratio of a product as it is actually used in medical practice.[11]

National spontaneous reporting schemes have successfully identified many new drug hazards. Examples include hepatotoxicity with the novel uricosuric diuretic tienilic acid[12], and anaphylactoid reactions with zomepirac[13] in the USA, and agranulocytosis with the antipsychotic agent clozapine[14] in Finland.

In the United Kingdom, novel adverse reactions identified through the yellow-card scheme include multi-system toxicity with the antimalarial agent *Fansidar*[15], hepatotoxicity and pulmonary fibrosis with amiodarone[16], Guillain-Barre syndrome with the antidepressant zimeldine[17], arthralgia with mianserin [18], oesophageal ulceration with emepromium bromide [19], and severe gastrointestinal, liver, blood and skin reactions with benoxaprofen.[20]

In addition to identifying new drug hazards, spontaneous reporting systems have also classified the clinical features of many reactions discovered by other means. Thus, reports of nitrofurantoin-induced eosinophilic pulmonary reactions from doctors in Sweden, Finland and the United Kingdom[21] provided valuable material for the clear clinical definition of this syndrome.

Spontaneous reporting of adverse reaction allows for a qualitative description of how the reaction affects patient's lives[22], Two vital advantages of surveillance systems based on spontaneous reporting are that they potentially maintain ongoing surveillance of all patients, relatively inexpensive and are most cost effective way to detect rare, serious adverse events not discovered during clinical trials.[23]

The main strength of the spontaneous reporting scheme is that it enables continual monitoring of the use of a product throughout its life span and by all patients.[23]

Under-reporting is the chief hitch in developed countries too where the Pharmacovigilance system is well recognized and practiced. Active reporting system and establishment of standardized approaches can ensure the prevention of ADRs. A huge role can be played by all healthcare professionals together with physicians, dentists, nurses and clinical pharmacists. This could be further improved through conducting educational programs lectures, newsletters, personalized letters, etc on spontaneous reporting.[24]

Recommendations

- It is the professional duty of all healthcare professionals to report all suspected ADR's and all serious ADRs associated with established products using the Yellow Card Scheme. If there is any uncertainty about whether a report should be submitted it is best practice to report the ADR. The experts assessing the report can then decide if further investigation is needed.

- All healthcare professionals should be vigilant to the status of medicines, particularly those which are under intensive monitoring, and changes to the classification of such medications such as pharmacy availability of former prescription only medicines.
- Healthcare professionals should not be deterred from reporting by the recently introduced provision for patients to report suspected ADRs.
- When prescribing medication, doctors should inform patients that should they suffer any reaction to a medication, they should inform the prescribing doctor.
- Patient information (leaflets etc) should be widely available in clinics in primary and secondary care explaining how patients can report ADRs.
- It is important that prescribers routinely ask patients about OTC medicines or herbal remedies they are using. This is particularly important in avoiding interactions which are a significant cause of ADRs.
- Effective communication between healthcare professionals is essential, as are comprehensive medical notes in order that doctors in different care settings have access to all the relevant information about a patient's medical history.

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SHORT COMMUNICATION

Pharmacovigilance of Ayurvedic Siddha and Unani Drugs and Provisions of Drugs and Cosmetics Act 1940

D K JAIN, RAJ KUMAR ARYA

GR Medical College, Gwallior - 474001 (India)

ABSTRACT

Drugs and cosmetics act, 1940 is an act to regulate the import, manufacture, distribution and sale of drugs and cosmetics. Section 3 (A) of chapter 1 of this act gives permission for manufacture, distribution and uses of Ayurvedic, Unani and Siddha drugs in accordance with the formulae described in the respective authoritative books, described in the Drugs in the Cosmetics Act. Study of efficacy of drugs is also a part of pharmacovigilance. In these systems of alternative medicine, active ingredients are not known, pharmacokinetic data's are not available and clinical controlled studies have not been done which indicate doubtful efficacy of these systems. Now, it is the duty of pharmacologists and other medicine specialists to put facts in front of Government and society. If lack of efficacy of these alternative systems of medicine has been proved then Government is ready to ban their manufacture, distribution and uses.

Key words: Drugs and Cosmetics Act 1940, Pharmacovigilance, Ayurved, Unani, Siddha, Efficacy

Drugs and Cosmetics Act, 1940[1] - Drugs and cosmetics act, 1940[1] is an act to regulate the import, manufacture, distribution and sale of drugs and cosmetics. Provisions of Chapter IV-A are related with Ayurvedic, Siddha and Unani drugs. This act extends to the whole of India. The provisions of chapter IV shall take effect in a particular state only from such date as the State Government may, by like notification appoint in this behalf. It is mandatory requirement that there must be two notifications, one under section 1(3) and another under section 18 to be published by the concerned State Government.

Section 3(a) of Chapter 1 of Drugs and Cosmetics Act - According to Section 3(a) of Chapter 1, Ayurvedic, Siddha or Unani drugs includes all medicines intended for internal or external use for or in the diagnosis, treatment, mitigation or prevention of disease or disorder in human being or animals, and manufactured exclusively in accordance with the formulae described in the authoritative books of Ayurveda, Siddha and Unani Tibb systems of medicine, specified in the first schedule.

Books Included in the First Schedule of Drugs and Cosmetics Act – Ayurvedic books included in the first schedule of Drugs and cosmetics Act are Fifty Four. Important book are : Ayurveda Prakasha, Ayurveda Samgraha, Bhaishajya Ratnavali, Bharat Bhaishajay Ratnakara, Bhava Prakasha, Brihat Nighantu Ratnakara, Charaka Samhita, Chakra Datta, Nighantu Ratnakara, Rasa RajaSundara, Rasaratna Samuchaya, Rasa Tarangini, Sharangadhara Samhita, Siddha Yoga Samgraha, Sushruta Samhita, Basava Rajeeyam, Ayurvedic Formulary of India, Ayurveda Sara Sangraha, Ayurvedic Pharmacopoeia of India.

Books of Siddha system of medicine included in the first schedule of Drugs and Cosmetics Act are thirty. Important books are Brahma Muni Karukkadai (300), Bhogar (700), Pulippani (500), Agashiyar Rathna Churukkam, Therayar Karisal (300), Agasthiyar (600), Yogi Vatha Kaviyam, Nagamuni (200), Agasthiyar Chillari Kovai, Yugi Karisal (151), Siddha Formulary of India (Part-I).

Books of Unani Tibb System included in the first schedule of Drugs and Cosmetics Act are fourteen. Important books are : Karabadin Kabir, Ilaj-ul-Amraz, Biaz kabir Vol. II, Karabadin Jadid, Kitab-ul-Taklis, Mifta-ulKhazain, Madan-ul-Aksir, Makhzan-ul-Murabhat, National Formulary of Unani medicine, Unani Pharmacopoeia of India.

Definition of Drugs Mentioned in Drugs and Cosmetics Act – "In Section 3B, definition of drug is mentioned. Drug includes:

(1) All medicines for internal or external use of human beings or animals and all substances intended to be used for or in the diagnosis, treatment, mitigation or prevention of any disease or disorder in human beings or animals including preparations applied on human, body for the purpose of repelling insects like mosquitoes. (2) Such substances (other than food) intended to affect the structure or any function of the human body or intended to be used for the destruction of vermins or insects which cause disease in human being or animals, as may be specified from time to time by the Central Government by notification in the official Gazette. (3) All substances intended for use as components of a drug including empty gelatin capsules. (4) Such devices intended for internal or external use in the diagnosis, treatment, mitigation or prevention of disease or disorder in human being or animals, as may be specified from time to time by the Central Government by notification in the official Gazette."[1]

Patent or Proprietary Medicines - Patent or proprietary medicines has been defined in this act. According to Section 3(h) of this act, patent or proprietary medicine means - (1) in relation to Ayurvedic, Siddha or Unani Tibb system of medicine, all formulations containing only such in gradients mentioned in the formulae described in the authoritative books of Ayurveda, Siddha or Unani Tibb systems of medicine specified in the first schedule, but does not include a medicine which is administered by parenteral route and also a formulation included in the authoritative books as specified in clause (a)

2. In relation to any other systems of medicine, a drug which is a remedy or prescription presented in a form ready for internal or external administration of human beings or animals and which is not included in the edition of the Indian Pharmacopoeia for the time being or any other pharmacopoeia authorised in this behalf by the Central Government after consultation with the Drugs Technical Advisory Board Constituted under section-5.

The Second Schedule Defines Homeopathic Medicines - These are drugs (1) included in the Homeopathic pharmacopoeia of India, (2) not included in the Homeopathic Pharmacopoeia of India but which are included in the Homeopathic Pharmacopoeia of United States of America or the United Kingdom or the German Homeopathic Pharmacopoeia, (3) not included in the Homeopathic Pharmacopoeia of India or the United States of America or the United Kingdom or the German Homeopathic Pharmacopoeia.

Second Schedule also Defines other Drugs: (1) Drugs included in the Indian Pharmacopoeia. (2) Drugs not included in the Indian Pharmacopoeia but which are included in the official Pharmacopoeia of any other country.

Pharmacovigilance and Efficacy of Drugs - In Ayurvedic, Siddha and Unani Systems 98 books are approved. Whatever written in these books, presumed to be correct. Drugs mentioned in these books are marketed without any scientific evaluation. Active ingredients are not identified in these medicines. Clinical controlled studies have not been done to evaluate efficacy. Pharmacokinetic data cannot be obtained without isolation of active ingredients, without pharmacokinetic study, doses cannot be determined, and relationship between doses and toxicity cannot be established.

Ayurvedic, Siddha, Unani and Homeopathic systems of therapeutic should not be accepted without scientific evaluation. These all have doubtful efficacy. "Analysis of Homeopathic principles on the basis of available knowledge of modern medical science, has suggested futility of Homeopathic system of therapeutics"[2] "Complementary and Alternative Medical practices (CAM) include Acupuncture, Ayurvedic Medicine, Dance Therapy, Massage, meditation, Naturopathy Siddha Medicine, Unani Medicine, Yoga, Homeopathy etc. None the less, over the past few decades, thousands of studies have been performed of various CAM approaches. To date however, no single approach has been proven effective in convincing way"[3]

"Good Pharmacovigilance practice refers to carefully planned and executed pharmacovigilance activities to minimize toxicity and maximize beneficial effects of drugs and biologicals"[4]

Unfortunately, there is still confusion on the work of pharmacovigilance. "Pharmacologists and other medical specialists think that pharmacovigilance is concerned only with side effects & toxic effects. It is absolutely wrong. When CAM is included in the pharmacovigilance, evaluation of efficacy of CAM should be the first duty in pharmacovigilance because efficacy of these systems is doubtful."[5]

"World Health Organization defines pharmacovigilance is

the science & activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems. Recently its concerns have been widened to include herbals, traditional & complementary medicines, blood products, biological medical devices & vaccines (W.H.O. 2002)"[6] "Adverse drug reaction or an adverse reaction means a response to a medicine in the humans or animals, which is noxious and unintended, including lack of efficacy, and which occurs at any dosage and can also result from an overdose, misuse or abuse of a medicine."[7] Therefore it is the duty of pharmacologists to study and discuss efficacy of substances used in alternative and complementary systems of medicine.

To Solve the Dilemma, New Concepts are Being Developed - To solve the confusion created by acceptance of alternative and complementary system of medicine, the definition of drug has been changed. Previously the definition of drug was as follow. "Drug is any substance or product that is used is intended to be used to modify or explore physiological systems or pathological states for the benefit of recipient."[8] Now, drug is not a substance or product. "It is a chemical substance of know structure, other than a nutrient or an essential dietary ingredient, which, when administered to a living organism, produces a biological effect."[9]

Medical knowledge is constantly changing. As new research and clinical experience broaden our knowledge, changes in concept and treatment may become necessary or appropriates. In the herbs, mentioned in the books of Ayurved, Siddha and Unani Systems of therapeutics, active chemical ingredients with known chemical structures are not known. Therefore they can not be considered as drugs "as clarified by the definition of drugs"[9]

"In United States of America herbal medicines have been regulated under the Dietary Supplement Health and Education Act (DSHEA) of 1994. On the basis of this law, herbal medicines are not evaluated by the FDA and most important, these products are not intended to diagnose, treat, cure or prevent diseases."[10]

That's why all herbal products of Ayurved, Siddha, and Unani system should not be labeled as medicines. These all products mentioned in Ayurved, Siddha and Unani system should be evaluated scientifically. Their active ingredients should be identified and isolated. After successful pharmacokinetic, pharmacodynamic and toxic studies in animals, clinical controlled study in human should be done to investigate benefit in diseases. After beneficial results only, they can be considered as medicines. In the absence of evidence of scientific study, product mentioned in these books can not be considered as medicines and their use should be prohibited.

Power of Central Government to Prohibit, Manufacture and Distribution of Drugs - According to chapter IV-A, Section 33EED of Drugs and Cosmetics act 1940, Power of Central Government to prohibit manufacture, etc, of Ayurvedic, Siddha or Unani drugs in Public interest without prejudice to any other provision contained in this chapter, if the Central Government is satisfied on the basis of any evidence or other material available before it that the use of any Ayurvedic, Siddha or Unani drug is likely to involve any risk to human being or animals or that any such drug does not have the therapeutic value claimed or purported to be claimed for it and that in the public interest it is necessary or expedient so to do then, that Government may by notification in the official Gazette, prohibit the manufacture sale or distribution of such drug.

"Under section 26A of Drugs and Cosmetics Acts 1940"[1], Central Government has power to prohibit the manufacture, sale, distribution of any drug or cosmetic. Without prejudice to any other provision contained in this Chapter, if the Central Government is satisfied, that the use of any drug or cosmetic is likely to involve any risk to human beings or animals or that any drug does not have the therapeutic value claimed or purported to be claimed for it or contains ingredients and in such quantity for which there is no therapeutic justification and that in the public interest it is necessary or expedient so to do, then, that Government may, by notification in the Official Gazette, prohibit the manufacture, sale or distribution of such drug or cosmetic.

Duty of Pharmacologists and Medicine Specialists- Now-a-days Ayurved, Homeopathy, Yoga, Unani and Siddha system of medicine are becoming popular in India and many other part of the world. The government of India is also supporting these systems of therapeutics which are unscientific, illogical, unreliable and not based on proper experimental work.

It is the most important and earnest duty of pharmacologists and medicine specialists to protect the society from the dangers being caused by the harmful

practices of unscientific and useless therapeutic systems. Crores of rupees are being spent on alternative system of medicine unnecessarily. Due to this tuberculosis, leprosy malaria and other curable diseases are spreading dangerously. Modern medical science is highly effective in these ailments but the use of alternative system of medicine makes them incurable and unbeatable and then it becomes death knell for the poor and uneducated people. At present, alternative systems of medicine, misguiding the public and society and increasing morbidity and mortality because it is interfering in application of modern medical science.

Therefore it is the duty of experts of modern medical science to put facts in front of the Government and society. Government has given protection to those specialist who are ready to tall these facts to Government.

According to Section 37 of Drugs and Cosmetics Act no suit prosecution or other legal proceedings shall lie against any person for any thing which is in good faith done or intended to be done under this act.

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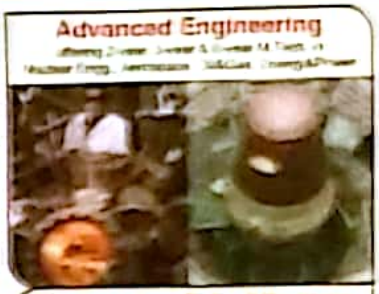

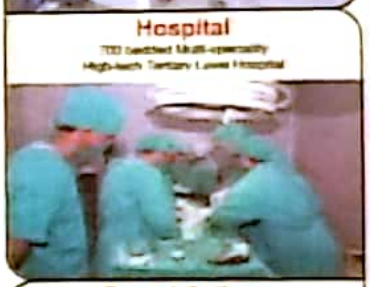

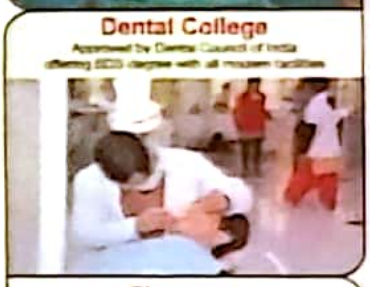

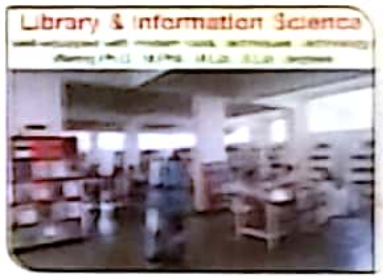

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