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Expecting the Unexpected — Adverse drug reactions (ADR)

Adverse reactions occurring within a short time of stopping or starting a particular drug are relatively less complicated to detect. They are often more readily suspected because of the close temporal relationship and are associated with a higher degree of biological and pharmacological plausibility. Pharmacovigilance work to detect problems which occur with a longer latency period involves cases where the cause of the reaction is far more difficult to ascertain.

Well established drugs may have the potential to cause serious problems after many years on the market. There are a variety of reasons for this phenomenon. It could be that medical records are not available, or that the patient cannot accurately remember how and when they were taking the product - and how and when they stopped. The relationship between the adverse event and the responsible medicine is less likely to be suspected by either the patient or their health professional, as there may be no clear logical, pharmacological or biological relationship apparent between taking the drug and the reaction arising. Suspicions between an Adverse Reaction occurring with a long latency period for a particular drug might only be detected by epidemiological means.

In real life, there have been cases where a drug has been very well established on the market before the potential to provoke the Adverse Reaction has been detected. A robust pharmacovigilance system is essential to ensure that manufacturers and drug regulators are correctly monitoring, evaluating and processing any reports associated with even the longest established products, even after the patent has expired.

Particular therapeutic approaches may also present a risk of long latency adverse reactions or delay in detection. Gene therapy may represent one example, whereby the permanent changes to recipient cells may be associated with toxicities which are detected many years later. There may also be cases where viral vectors are used, raising the possibility of whether the potential exists for a latent infection to clinically manifest itself some years later. Antiretrovirals have also been studied and found to sometimes be associated with multiple late onset problems related to toxicity. Long term follow up clinical trials are of paramount importance; controlled comparisons and epidemiological methods such as prospective cohort studies can be carried out in such instance.

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

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XIIth Annual Conference of Society of Pharmacovigilance (India) (SOPICON - 2012)

Date : Pre-conference workshop on 23rd November, 2012
Conference on 24th & 25th November, 2012
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Pharmacovigilance in India: A Collaborative Approach

YOGESH MURTI*, BHUPESH CHANDER SEMWAL

Institute of Pharmaceutical Research, GLA University, N.H.2, Delhi-Mathura Bye-pass Mathura-281406

ABSTRACT

Pharmacovigilance is still in its infancy in India and there exists very limited knowledge about the discipline. India is the fourth largest producer of pharmaceuticals in the world and is also emerging as a clinical trials hub. Many new drugs are being introduced in the country, so there is an immense need to improve the pharmacovigilance system to protect the Indian population from potential harm that may be caused by some of the new drugs. If we work together, we can build a world-class pharmacovigilance system in India with the help of collaborative approach. Sustained collaboration and commitment are vital if the future challenges in pharmacovigilance are to be met and the discipline is to continue to develop and flourish. A properly working pharmacovigilance system is essential if medicines are to be used safely in India. The outcome of a pharmacovigilance system in India definitely decreases ~~medicine-related problems with the ultimate impact being a reduction in morbidity and mortality.~~

Key word : Pharmacovigilance, WHO, Collaboration, Partners, India

Introduction

When a pharmaceutical drug is introduced in the market there are still a lot of things that are unknown about the safety of the new drugs. These medicines are used by various patients for different diseases. These people might be using several other drugs and must be following different traditions and diets which may adversely affect the impact of medicine in them. Also the different brands of same medicine might differ in the manner of their production and ingredients. Additionally, adverse drug reactions might also occur when drugs are taken along with traditional and herbal medicines that have also to be monitored through pharmacovigilance. In some cases, adverse drug reaction of certain medicines might occur only in one country's or region's citizens. To prevent all undue physical, mental and financial suffering by patients, pharmacovigilance proves to be an important monitoring system for the safety of medicines in a country involving collection, monitoring, researching upon, assessing and evaluating information received with the support of health care workers such as doctors, pharmacists, nurses and other health professionals for understanding the adverse drug reaction. This paper focuses on the efforts and endeavors of India to create an efficient medication error

reporting systems to ensure public safety [1]. Health care professionals, policy makers, federal agencies and the government need to work in harmony in order to gain public assurance, safety and trust [2].

Aims of Pharmacovigilance

The principal aims of pharmacovigilance programmes are [3-6]:

1. Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions.
2. Contribute to the assessment of benefit, harm, effectiveness, and risk of medicines, encouraging their safe, rational, and more effective (including cost-effective) use.
3. Promote understanding, education, and clinical training in pharmacovigilance and its effective communication to the public.
4. Detect problems related to the use of medicines and communicate the findings in a timely manner.
5. To promote rational use of medicines by providing

information about ADRs.

6. Provide regulators with the necessary information to amend the recommendations on the use of the medicines.
7. Identification, quantification and improving understanding of previously unknown adverse drug reactions.
8. Identification of patients at particular risk of having an ADR (For e.g. the elderly, children, hepatic and renal compromised patients and terminally ill patients).
9. Educate health professionals to understand the effectiveness/risk of medicines that they prescribe.
10. Monitoring the impact of any action taken.

Pharmacovigilance in India

Pharmacovigilance program is useful in helping healthcare organizations and practitioners across India to use medicines more safely. Efforts are now being taken in India to set up a pharmacovigilance system, which can collect information on ADR's [7]. In the recent years, India has seen the establishment of a society for pharmacovigilance, which aims at "establishing pharmacovigilance as a distinct and influential clinical discipline in India" [8].

India also has 30 pharmacovigilance centers funded by World Bank. These centers are scanning instances of adverse drug reaction since January 2005. These 30 centers form a network of regional and peripheral centers at medical colleges in several states and are responsible for collecting and interpreting the data, and for reporting their findings to the drug controller general of India [9].

Advantages in India

The Pharmaceutical industry in India is valued at Rs. 900,000 million and is growing at the rate of 12-14 % per annum. Exports are growing at 25 % Compound Annual Growth Rate (CAGR) every year. India is now being recognized as the 'Global Pharmacy of Generic Drugs' and has distinction of providing quality generic drugs at affordable cost. India is also emerging rapidly as a hub of Global Clinical trials & a destination for Drug Discovery & Development. Further, more & more new drugs are being introduced into the country which include New Chemical Entities (NCEs), high tech pharmaceutical products, vaccines as well as new dosage forms, new

routes of drug administration and new therapeutic claims of existing drugs. Such rapid induction of NCEs and High-tech Pharmaceutical products in the market throw up the challenges of monitoring ADRs over large population base.

All drugs (pharmaceuticals and vaccines) have side effects. Some of these side effects are known, while many are still unknown even though the drug has been in clinical use for several years. It is important to monitor both the known and unknown side effects of drugs in order to determine any new information available in relation to their safety profile. In a vast country like India with a population of over 1.2 billion with ethnic variability, different disease prevalence patterns, practice of different systems of medicines, different socioeconomic status, it is important to have a standardized and robust pharmacovigilance and drug safety monitoring programme for the nation. Collecting this information in a systematic manner and analyzing the data to reach a meaningful conclusion on the continued use of these medicines is the rationale to institute this program for India [10].

Future of Pharmacovigilance in India

The development of pharmacovigilance within a public health programme should be seen as an important opportunity for the development within the local health service of a comprehensive national pharmacovigilance system and should be seen as an obligatory investment in the future public health of the territory [11]. It is of utmost importance that the monitoring, evaluating and communicating drug safety should be a collective responsibility of consumers, health professionals, researchers, academia, media, pharmaceutical industry, drug regulators, governments and international organizations. The working should be of high scientific, ethical and professional standards and a moral code should govern this activity [12]. Figure 2 gives the roadmap for implementation of the pharmacovigilance programme of India.

Key Partners in Pharmacovigilance

The management of the risks associated with the use of medicines demands close and effective collaboration between the key players in the field of pharmacovigilance. Sustained commitment to such collaboration is vital, if the future challenges in pharmacovigilance are to be met, and the discipline is to

continue to develop and flourish. Those responsible must jointly anticipate, describe and respond to the continually increasing demands and expectations of the public, health administrators, policy officials, politicians and health professionals. However, there is little prospect of this happening in the absence of sound and comprehensive systems which make such collaboration possible. The constraints typically include lack of training, resources, political support, and most especially scientific infrastructure. Understanding and tackling these are an essential prerequisite for future development of the science and practice of pharmacovigilance [5].

A complex and vital relationship exists between wide ranges of partners in the practice of drug safety monitoring. The partners concerned, and the present constraints under which they function, are:

- Government
- Pharmaceutical industry
- National pharmacovigilance centers
- Hospitals and academia
- Medical and pharmaceutical associations
- Poisons and medicines information centers
- Health professionals (Doctors, Pharmacists,
- Nurses, Midwives and others)
- Patients
- Consumers
- The media
- World Health Organization

The constraints include training, resources, political support, and most especially scientific infrastructure. Understanding and tackling these would set the scene for future development of the science and practice of pharmacovigilance. Public awareness about adverse reactions, early reporting and management are essential for ensuring patient confidence, in and adherence to, pharmacotherapy. Patient education is an important role of the primary health-care provider. Educating the public on

important to achieve a positive attitude towards pharmacovigilance. It is the responsibility of the primary health-care provider to detect, investigate, manage and report ADRs. These staff will need training on the importance of adverse reactions, diagnosis, and the basic principles of causality assessment and the important elements of the adverse reactions reporting form. Health care providers should be offered basic education in the law and the legal process surrounding ADRs to reduce some of the anxiety about possible legal action. All health professionals must take responsibility for quality control and optimizing quality of drug therapy. To this end, they should be reminded of their duty to report ADRs as a part of their professional responsibility and daily work. They must be informed about what to report, how to report, to whom to report, and that proof of causality is not a precondition for ADR reporting. Educational programmes in ADR reporting should be established in hospitals in collaboration with the hospital pharmacists. Members of ethics committees should have special training in pharmacovigilance [13]. The efforts of pharmacology and clinical pharmacy departments around the world have resulted in the development of pharmacovigilance as a clinical discipline. A number of medical institutions have developed adverse reaction and medication error surveillance systems in their clinics, wards and emergency rooms. The role of a clinical pharmacist in the establishment of a medication error reporting system at each hospital and to share the data with other hospitals/healthcare settings appears to be a strong intervention; and, the clinical pharmacist, initially, could only confine to identification of the medication errors [14].

The district investigation team plays a central role in monitoring adverse reactions. The team should comprise a clinicians in the district hospital, head nurse, pharmacist and district health officer or programme manager. Harm-benefit evaluation and pharmacovigilance should be part of the professional training of nurses, midwives, healers and other health professionals. They have to be actively included in reporting of ADRs. The team is responsible for following up adverse reactions reported from all the health facilities within their district. The team will play an important role in collaboration with and encouragement of reporting by primary health centre staff and hospital staff. The district health officer or programme manager will coordinate the investigation, report to the national pharmacovigilance coordinator, and contribute to the education of clinical staff and the public on medicine

safety. The national coordinator should ensure harmonization of pharmacovigilance in public health with other national pharmacovigilance activities, promote the reporting form, and develop a national database for signal generation [11].

Pharmaceutical manufacturers are legally responsible for the safety and effectiveness of medicines while the product is available in the marketplace. They have a duty towards assessing the effectiveness and safety of a public health programs and the benefits to patients. They should report adverse reactions both to the national pharmacovigilance centre. The pharma industry needs to strengthen safety monitoring during clinical trials by involving independent pharmacovigilance experts in the early phase of study design. Declaration of conflicts of interest of investigators is now obligatory and should be made public. Postmarketing surveillance of recently marketed drugs have to be non-interventional: there should be no deliberate change of treatment in postmarketing studies for marketing or promotional reasons merely to recruit the patient into the study [13].

From the beginning of therapy, patients must be informed independently and fully about the potential benefits and harms of therapy. The factors that influence the ways in which individuals respond to information about health risks and whether patients understand the information supplied should be explored [15]. Patients should be helped to recognize ADRs, and to inform their physician and/or other health professionals about suspected ADRs and other drug problems. Health professionals should encourage spontaneous reporting of drug-related harm by patients (including volunteers who take part in drug trials), to pharmacovigilance centers, special centers for patients/consumers or directly to health authorities. The use of telephone hotlines or online reporting via the internet needs to be evaluated. Specially written, clear and user-friendly reporting forms should be made available, for instance in pharmacies, to facilitate ADR reporting by patients. Patient reporting systems should periodically sample and evaluate the scattered drug experiences patients report on the internet. Patient organizations reporting ADRs should have in place an appropriate structure to validate reports [13].

The media have an important role in creating awareness in the community and among professionals. The Erice declaration urges all players, including the media, to strive towards the highest ethical, professional, and scientific

standards in promoting the safe use of medicines. WHO has made considerable efforts to train medicine regulators and national immunization staff in communicating information to the media on adverse events following immunization. It is important that the media are involved from the start of a public health programs and that the need for the programme is publicized together with the need for pharmacovigilance. It is useful to assess the impact of media communications on public awareness and attitudes as this will assist the development of future communication strategies.

At an international level WHO will play a key role. While supporting countries to conduct public health programs, WHO and its regional offices have a responsibility to promote the establishment and building of sustainable safety monitoring systems. WHO will take a lead role in supporting Member States in the safe use of medicinal products. WHO will serve as a repository for information from both pharmacovigilance programmes and public health programs, and will disseminate this information appropriately. It will promote and encourage uniformity of terminology and will promote and develop resource materials and provide leadership in training and capacity development [11].

Healthcare is a diversified field comprising of a myriad and complex professional hierarchy, infrastructure, policies, rules and regulations. A proper leadership which fosters a work culture of safety from the grass root to the acme of a healthcare organization is essential [16,17]. Partners in pharmacovigilance have directly or indirectly facilitated the development of new and robust drug policies and decisions, while highlighting deficiencies and weaknesses in existing drug safety policies. In many instances these groups or individuals have the capacity to voice, and often change public opinion. Moreover, they often facilitate active public debate and discussion of issues, which have direct relevance to their health. Co-operation and open lines of communication with non-governmental agencies including the media and consumer advocacy groups is likely to facilitate the creation of policies and legislation on pharmacovigilance which will enjoy widespread public support and confidence.

Development of Pharmacovigilance

The introduction of automation into medical and pharmaceutical practice administration and progress in computing technology are likely to lead to drastic changes in the routines of pharmacovigilance. Additional funds are

needed for their further development and structural use in pharmacovigilance. In coming years, the following issues may be come of special interest in the development of pharmacovigilance [18].

- Improvement of national spontaneous reporting systems.
- The development or improvement of additional methods in pharmacovigilance, especially with regards to the study of type C ADRs.
- Intensification of the scientific study of medicines after approval, e.g. for signal testing, frequency estimation of adverse reactions, identification of risk determinants and elucidation of reaction mechanisms.
- In the midst of different and possibly conflicting interests, pharmacovigilance needs a climate of independence, whether scientific, political or financial, to allow for due collection and assessment of the data. On the other hand, the system must be as transparent as possible to ensure public confidence.
- The ultimate aim of pharmacovigilance is that new information be rapidly and effectively incorporated into therapeutic decision-making by physicians, pharmacists and patients, by drug information professionals and formulary committees, by regulators and by pharmaceutical companies. Most comprehensive and efficient pharmacovigilance should further improve the safe introduction of new medicines and foster rational pharmacotherapy.

The Next Step: International collaboration

The principle of international collaboration in the field of pharmacovigilance is the principal basis for the WHO International Drug Monitoring Programme, through which over 90 member nations have systems in place which encourage healthcare personnel to record and report adverse effects of drugs in their patients. These reports are assessed locally and may lead to action within the country. Through membership of the WHO Programme one country can know if similar reports are being made elsewhere [19].

The National Pharmacovigilance Program collects, collate, analyze and monitors data to identify any unexpected or suspected ADRs which is then further

reported to WHO International Drug Monitoring Programme for international collaboration on drug safety. The core of data generating system of international Pharmacovigilance program is spontaneous reporting [20]. Member countries send their reports to the Uppsala Monitoring Centre where they are processed, evaluated and entered into the WHO International Database. When there are several reports of adverse reactions to a particular drug this process may lead to the detection of a signal - an alert about a possible hazard communicated to member countries. This happens only after detailed evaluation and expert review [21].

Conclusion

The integration of pharmacovigilance may be crucial to the success of public health programmes using medicines. Due to high consumption of medicines and self-treatment by all, especially the aging population, the issue of proper medication use and safety is at the forefront of public health concerns globally. Each country has a different approach towards medication event monitoring that is compliant with its own health care system. Development of these systems may eventually contribute to a global medication vigilance system, which could reduce concern with medication errors and safety. Since, there are considerable social and economic consequences of ADRs there is a need to engage health-care professionals, in a well structured programme to build synergies for monitoring ADRs. The purpose of the pharmacovigilance program of India is to collect, collate and analyze data to arrive at an inference to recommend regulatory interventions, besides communicating risks to healthcare professionals and the public.

Much needs to be done to improve the relationship between partners in pharmacovigilance. Misrepresentation of data and sensationalism of drug safety concerns in the media and in courtrooms has given rise to unfounded rumors and misplaced concerns about the safety of potentially valuable medicines. Situations where there has been divergence in perspective on specific issues of safety between partners, have resulted in a devastating impact on public confidence in regulatory bodies and other organizations. It is important that all partners recognize the considerable responsibility inherent in conducting activities relating to pharmacovigilance and of communicating them effectively.

The pharmacovigilance practice cannot be achieved without practical and lively communication. This involves

a wide range of knowledge and skills which are often neglected. There is a need of critical examination of the strengths and weaknesses of both pharmacovigilance systems and public health systems. So, health care professionals, e.g. physicians, pharmacists, nurses, and officials, academics or industry employees who have recently become engaged or soon will become engaged in the practical operation of pharmacovigilance programmes in a hospital, community, regulatory, university or industry setting, or in public health programmes have to be proactive on many fronts and should always remember, "Coming together is a beginning; keeping together is progress; working together is success".

"The person who takes medicine must recover twice, once from the disease and once from the medicine."

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Drug Interactions of General Anesthetics: A Review

VIVEK SRIVASTAVA^{*1}, VIMLESH MISRA¹, BHUPESH CHANDER SEMWAL¹,
SHEIKH MUBEEN UDDIN¹, GOVIND MOHAN²

¹Dept of Pharmacology, IPR, GLA University, Mathura
²NIMS Institute of Pharmacy, NIMS University, Jaipur.

ABSTRACT

A drug interaction is a condition in which a substance affects the activity of a drug, i.e. the effects are increased or decreased, or they produce a new effect that neither produces on its own. The present review shows the various interactions of general Anesthetics. General anesthetic is a drug that brings about a reversible loss of consciousness. These drugs are generally administered by an anesthesia provider to induce or maintain general anesthesia to facilitate surgery. The various drugs used as general anesthetics are Atracurium, Atropine, Diazepam, Etomidate, Halothane, Isoflurane, Lignocaine, Neostigmine, Propofol, Sevoflurane, Thiopental, Ketamine, Vecuronium etc. It is found that these drugs should be used very carefully and in a suitable dose at the time of the surgery otherwise it may give rise to some serious consequences.

Key word : Drug Interactions, Adverse drug Interaction, Ketamine, Propofol, Diazepam, Thiopental, Lignocaine

Introduction

In the recent years, a number of new general anesthetic products have been introduced in the market, with increasing frequency. But the question is that whether the new drug will interact with any of their routine medicines of the patient.

The Boston collaborative drug surveillance program reported a study of 9,900 patients with 83,200 drug exposures and found 3,600 adverse drug reactions, 234(6.5%) of which were attributable to drug interactions.¹

Each year number of death occurs as the direct result of patient a new drug in combination with their existing medication regimen. The small number of drug is withdrawn from the market annually due to their ADRs, or drug interactions. Although many ADRs are detected during clinical trials, the side effects profile of a new drug often require more extensive use of including use by patient population who may not have been adequately represented in the drug's clinical trials. Many drugs are generally studied in young, healthy patients who are not taking other medication. Consequently, it may take several months or years before adequate documentation of a problem exist. Adverse drug reactions² and drug

interactions present alarming problem to a vast majority of population and must be addressed by all healthcare providers.

In a study where the medical chart of 1,800 surgical patients were reviewed, researchers found at least one drug interaction in 17% of patients². other studies determined that 19% of nursing home patients received combinations of drugs with known harmful interactions³, and adverse drug reaction on medicine words in hospital resulted from drug interactions in 22% of patients⁴. In the study of clinical outpatients a slightly higher adverse drug reactions percentage of 23% was reported⁵. Drug interactions present a health risk to patients and medical challenge for pharmacist and physician.

General anesthetics

General anesthetic is a type of anesthesia, that causes loss of sensation. It is used to give pain relief during surgery. General anesthetic makes person completely loss of consciousness so that surgery can be carried out without causing any pain or discomfort. Examples are Atracurium, Halothane, Isoflurane, Ketamine, Lignocaine, Thiopental etc.

Atracurium

Atracurium is a neuromuscular-blocking drug or skeletal muscle relaxant in the category of non-depolarizing neuromuscular-blocking drugs, used adjunctively in anesthesia to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation. Atracurium is classified as an intermediate-duration non-depolarizing neuromuscular-blocking agent.

Interactions

1. Atracurium action is prolonged by the enflurane⁶
2. Midazolam prolong the recovery from the effect of atracurium by about 20%.⁷
3. Atracurium given to the patient taking β -blocker develops bradycardia.⁸
4. Recovery time from the intravenous atracurium is shorter in patients taking long term carbamazepine.⁹
5. Premedication with ephedrine did not significantly alter the onset of action of the atracurium.¹⁰
6. Prolongation of the neuromuscular blockage when given with cyclosporine.¹¹

Atropine

Atropine is a naturally occurring tropane alkaloid extracted from deadly nightshade (*Atropa belladonna*), Jimson weed (*Datura stramonium*), mandrake (*Mandragora officinarum*) and other plants of the family Solanaceae. It is a secondary metabolite of these plants and serves as a drug with a wide variety of effects. It is a competitive antagonist for the muscarinic acetylcholine receptor types M1, M2, M3, M4 and M5.

Interactions

1. Antihistaminics, antipsychotics, antiparkinson, alphaprodine, buclizine, meperidine, tricyclic antidepressants increases the anticholinergic effect of atropine and its derivatives.
2. Atropine increases vagal blockage.
3. Nitrfuran and thiazides diuretics increases the bioavailability.

Diazepam

Diazepam, first marketed as Valium is a benzodiazepine

drug. Diazepam is also marketed in Australia as Antenex. It is commonly used for treating anxiety, insomnia, seizures including status epilepticus, muscle spasms (such as in cases of tetanus), restless legs syndrome, alcohol withdrawal and benzodiazepine withdrawal. It may also be used before certain medical procedures (such as endoscopies) to reduce tension and anxiety, and in some surgical procedures to induce amnesia. It possesses anxiolytic, anticonvulsant, hypnotic, sedative, skeletal muscle relaxant, and amnestic properties. The pharmacological action of diazepam enhances the effect of the neurotransmitter GABA by binding to the benzodiazepine site on the GABA_A receptor (via the constituent chlorine atom) leading to central nervous system depression.

Interactions

1. Diazepam and ketamine decreases the hemodynamic effects.¹²
2. Diazepam prolong the duration of activity of gallamine.¹³

Etomidate

Etomidate is a short acting intravenous anesthetic agent used for the induction of general anaesthesia and for sedation for short procedures such as reduction of dislocated joints, tracheal intubation and cardioversion. It was discovered at Janssen Pharmaceutica in 1964 and it was introduced as an intravenous agent in 1972 in Europe and in 1983 in United States.

Interactions

1. Etomidate prolong the anesthesia and cheyne-stokes respiration when etomidate is given with verapamil.¹⁴
2. The etomidate action is enhanced by opioid analgesic and the dose requirement of etomidate may be lower after opioid use.¹⁵

Halothane

Halothane is an inhalational general anesthetic. Its IUPAC name is 2-bromo-2-chloro-1,1,1-trifluoroethane. It is the only inhalational anesthetic agent containing a bromine atom; there are several other halogenated anesthesia agents which lack the bromine atom and do contain the fluorine and chlorine atoms present in halothane. It is colorless and pleasant-smelling, but unstable in light. It is a

potent anesthetic with a minimum alveolar concentration of 0.74. Its blood gas coefficient of 2.4 makes it an agent with moderate induction and recovery time. It is not a good analgesic and its muscle relaxation effect is moderate.

Interactions

1. Combination of the halothane and catecholamine is sensitive to myocardium¹⁶
2. Midazolam potentiate the anesthetic action of the halothane.¹⁷
3. Ventricular arrhythmias is developed in patients anesthetized with halothane¹⁸
4. There is marked reduction in the cardiac performance with propranol.¹⁹
5. Halothane causes the enhanced hypotension with intravenous nimodipine²⁰
6. Halothane cause phenytoin toxicity with phenytoin by increasing the plasma level of phenytoin.²¹
7. Cardiac arrhythmias can develop during the concurrent use of the halothane and aminophylline²²
8. Halothane causes cardiac arrhythmia with tricyclic antidepressant.²³

Isoflurane

Isoflurane is a halogenated ether used for inhalational anesthesia. Together with enflurane and halothane, it replaced the flammable ethers used in the pioneer days of surgery. Its name comes from being a structural isomer of enflurane, hence they have the same empirical formula. It is a racemic mixture of (R) and (S) optical isomers. Its use in human medicine is now starting to decline, being replaced with sevoflurane, desflurane and the intravenous anesthetic propofol. Isoflurane is still frequently used for veterinary anesthesia.

Interactions

1. Cocaine and isoflurane combination causes ventricular fibrillation.²⁴
2. Pretreatment with anthracyclines may result in prolongation of the QT interval during isoflurane anesthesia.²⁵
3. Esmolol decreases the required dose of the isoflurane²⁶

4. Dexmetodine may reduce the dose requirement of the isoflurane²⁷
5. Isoniazid may increase the metabolism of the isoflurane and thereby increase the plasma fluoride concentration.²⁸
6. Phenylephrine eye drop given to patients undergoing isoflurane anesthesia causes marked cyanosis and bradycardia in baby and hypertension in women²⁹

Lignocaine

Lignocaine is a common local anesthetic and antiarrhythmic drug. Lignocaine is used topically to relieve itching, burning and pain from skin inflammations, injected as a dental anesthetic or as a local anesthetic for minor surgery. The efficacy profile of lignocaine as a local anesthetic is characterized by a rapid onset of action and intermediate duration of efficacy. Therefore, lignocaine is suitable for infiltration, block and surface anesthesia

Interactions

1. Lignocaine with aminoglycoside increases the neuromuscular blockage.
2. Cimetidine decreases the clearance of lignocaine and causes toxicity.

Neostigmine

Neostigmine is a parasympathomimetic that acts as a reversible acetylcholinesterase inhibitor. By interfering with the breakdown of acetylcholine, neostigmine indirectly stimulates both nicotinic and muscarinic receptors. Unlike physostigmine, neostigmine has a quaternary nitrogen; hence, it is more polar and does not enter the CNS. Its effect on skeletal muscle is greater than that of physostigmine, and it can stimulate contractility before it paralyzes. Neostigmine has moderate duration of action, usually 2 to 4 hours.

Interactions

1. Lignocaine with aminoglycoside increases the neuromuscular blockage.
2. Corticosteroids decrease the effect of the neostigmine.

Propofol

Propofol is a short-acting, intravenously administered

hypnotic agent. Its uses include the induction and maintenance of general anesthesia, sedation for mechanically ventilated adults, and procedural sedation. Propofol is used for induction and maintenance of anesthesia, having largely replaced sodium thiopental for this indication. Propofol is also used to sedate individuals who are receiving mechanical ventilation. In critically ill patients it has been found to be superior to lorazepam both in effectiveness as well as overall cost; as a result, the use of propofol for this indication is now encouraged whereas the use of lorazepam for this indication is discouraged. Propofol is also used for sedation, for example, prior to endoscopic procedures, and has been found to have less prolonged sedation and a faster recovery time compared to midazolam.

Interactions

1. Cocaine and propofol combination causes convulsions, increases the risk of the cardiovascular complications.³⁰
2. Propofol inhibit the CYP3A4 mediated metabolism of the ropivacaine³¹
3. Physostigmine and propofol combination increases the propofol requirement by 20%.³²
4. Metoclopramide pretreatment reduces the dosage requirement of propofol by 24%³³
5. Patient taking baclofen had severe seizures during induction of anesthesia with propofol.³⁴
6. Midazolam and propofol combination increases the anesthetic and hypnotic effect.³⁵
7. Clonidine significantly attenuates the response to hypercapnia in patients anesthetized with propofol.³⁶
8. Melatonin with propofol slightly reduces the dose of propofol needed for the induction of anesthesia.³⁷
9. Paracoxib does not affect Pharmacokinetics or clinical effects of propofol³⁸
10. Propofol causes the spontaneous movement of the upperlimbs in patients taking Selective serotonin reuptake inhibitors.³⁹

Sevoflurane

Sevoflurane (1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy) propane), also called fluoromethyl hexafluoroisopropyl ether, is a sweet-smelling, nonflammable, highly

fluorinated methyl isopropyl ether used for induction and maintenance of general anesthesia. Together with desflurane, it is replacing isoflurane and halothane in modern anesthesiology. It is often administered in a mixture of nitrous oxide and oxygen. After desflurane, it is the most volatile anesthetic with the fastest onset and offset.

Interactions

1. Alcohol taken with sevoflurane increases the risk of renal damage.⁴⁰
2. Sevoflurane with alfuzosin causes hypertension⁴¹
3. It impair the efficacy of anticholinesterase in reversing neuromuscular blockage.⁴²
4. Sevoflurane inhibit the platelet aggregation caused by the aloe vera⁴³
5. Premedication with oral tizanide appears to reduces the MAC of sevoflurane.⁴⁴

Thiopental

Thiopental is a rapid-onset short-acting barbiturate general anaesthetic. Thiopental is a core medicine in the World Health Organization's "Essential Drugs List", which is a list of minimum medical needs for a basic healthcare system. Thiopental is an ultra-short-acting barbiturate and has been used commonly in the induction phase of general anesthesia. A normal dose of thiopental (usually 4–6 mg/kg) given to a pregnant woman for operative delivery (caesarian section) rapidly makes her unconscious, but the baby in her uterus remains conscious. However, larger or repeated doses can depress the baby.

Interactions

1. Thiopentone with alcohol require more dose of the Thiopentone to achieve anesthesia than in non drinkers.⁴⁵
2. Metoclopramide reduces the Thiopentone requirement upto 41%.⁴⁶
3. Delayed recovery of the patient taking clozapine after short duration anesthesia induced by Thiopentone.⁴⁷
4. Sedative property of the antipsychotic is enhanced by Thiopentone⁴⁸
5. The anesthesia dose of the thiopentone is reduced by

pretreatment with aspirin.⁴⁹

6. It cause synergism with midazolam.⁵⁰
7. Kava potentiates the effects of the thiopentone⁵¹
8. The anesthetic dose of the Thiopentone is reduced and effect is prolonged by the pretreatment of probenicid.⁵²
9. Sulfonamides reduces the required anesthetic dose of the thiopentone by 36%⁵³.

Ketamine

Ketamine is a drug used in human and veterinary medicine. ketamine is classified as an NMDA receptor antagonist. Ketamine has a wide range of effects in humans, including analgesia, anesthesia, hallucinations, elevated blood pressure, and bronchodilation. Ketamine is primarily used for the induction and maintenance of general anesthesia, usually in combination with a sedative. Other uses include sedation in intensive care, analgesia (particularly in emergency medicine), and treatment of bronchospasm. It has been shown to be effective in treating depression in patients with bipolar disorder who have not responded to other anti-depressants.

Interaction

1. Levothyroxine develops marked hypertension and tachycardia when they were given with ketamine.⁵⁴
2. Nausea, vomiting dehydration and difficulty in sedation to the methylphenidate taking patients.⁵⁵
3. The respiratory depressant action of ketamine is enhanced by the morphine.⁵⁶

Vecuronium

Vecuronium (Norcuron) is a muscle relaxant in the category of non-depolarizing blocking agents. Vecuronium bromide is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation. Although vecuronium bromide is often thought of as a muscle relaxant, it may be more accurate to classify it as a paralyzing agent.

Interaction

1. Salbutamol injection increases the neuromuscular blockage of the vecuronium by 66% to 86%.⁵⁷
2. Bradycardia develops when vecuronium is given to

β -blocker taking patient.⁵⁸

3. Diltiazem decrease the vecuronium requirement by upto 50% for the induction of neuromuscular blockage.⁵⁹
4. Carbamazepine shortens the recovery time from vacuronium blockage in adults and in childrens.⁶⁰
5. Disopyramide may oppose the effect of the neostigmine used to reverse the neuromuscular blockage with vecuronium.⁶¹
6. H₂ blocker such as cimetidine significantly prolong the recovery from vecuronium.⁶²
7. Metronidazole increases the neuromuscular blockage effect of vecuronium.⁶³

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G6PD Deficiency and Leprosy : Dapsone Does Require A Revisit

RR PATHAK¹, S RAWAT², DS MAPARA¹

¹Department of Pharmacology, C U Shah Medical College, Surendranagar, Gujarat -363001

²Department of Physiology, SMS Medical College, Jaipur.

ABSTRACT

Dapsone is the most important ingredient of anti-leprosy regimes. Unless a clear-cut resistance is established or a severe drug reaction befalls, any regime is hardly modified to avoid it. But G6PD (Glucose-6-Phosphate Dehydrogenase) deficiency can be the third reason to think of a similar modification. This strategy is even more relevant considering, more than 2/3 Indians as slow acetylators (hence expected high plasma level of sulfones like dapsone) and protracted course of treatment. In the present study prevalence of G6PD deficiency in Gujarat has been determined community-wise employing a simple screening procedure for G6PD with the view to highlight a heretofore "neglected adjustment" for dapsone dosage and/or prescribing alternate topical preparations in the leprosy treatment guidelines for those with G6PD deficiency and hence are prone to severe haemolysis.

Key word : G6PD, Leprosy, Dapsone, Acetylator, Genetic Polymorphism

Introduction

Dapsone is a sulfone and metabolized by acetylation which can vary among individuals as per genetic make-up (Petri, 2006) (slow and fast acetylators are widely recognized categories). Indians are mostly (more than 2/3) slow acetylators (Roy et al, 2010; Babu et al, 2004) and thus the higher level of dapsone is expected. Sulfones have been shown to induce hemolysis in G6PD deficient people (Chernof 1967; Banait et al 1971; Saha et al, 1971).

Direct effect on incidence or prevalence of leprosy infection has not been studied in G6PD deficient people widely. But as higher dapsone levels are expected in majority of Indians due to their slow acetylating status, the long duration treatment of leprosy with dapsone could make an adverse impact in this genetically deficient leprosy patient group. There are only scanty reports in this perspective – only two from India (Chernof, 1967; Banait & Junnakar, 1971; Saha et al, 1971; Mysore et al, 1999; Scott et al, 2008; Garrett, 2009). Highly inbred populations (e.g. maritally isolated/ orthodox society) have shown more prevalence of genetic anomalies (Babbitt, 2006), and it was thought worthwhile to enlist the subjects of this study community-wise.

For G6PD status evaluation the present study has, therefore, been undertaken with the twin objectives of:

- Deciding the status of G6PD deficiency in leprosy patients by designing and carrying out a G6PD-screening of the visiting subjects in the catchment area of C U Shah Medical College (CUSMC), Surendranagar, Gujarat and enlisting them community-wise.
- Analyzing and evaluating the quantity of risks and consequences of such incidence of G6PD deficiency combined with the use of an exemplary oxidizing drug like dapsone in the area as endorsed by the relative extent of dapsone dispensing in the hospital.

Materials & Methods

One hundred fifty patients (78 males and 62 females) who visited C U Shah Medical College Hospital (CUSMC), Surendranagar, Gujarat and prescribed dapsone were included in this study with the following exclusion criteria: a) History of recent hemolysis as evidenced by the incidence of smoky black urine within past 15 days and significant reticulocytosis at the time of presentation b) Anemia at the time of the study – Subjects with

hemoglobin level < 10 gm/ dL were excluded (Sood & Rusia, 1986). The patients' personal history (current Hb, recent hemoglobinuria) and demographic data (age, sex, community) were recorded. Anticoagulated (EDTA added) blood was collected for evaluation of G6PD status.

The standard screening method described by Godkar & Godkar (2003) was used. The principle of the method is that due to an increase in acidity (decreasing the pH) through production of H^+ ions in the presence of G6PD from hemolysed blood, bromocresol blue reagent [8 parts of bromocresol blue - 16mg/dl in Tris buffer solution(0.5 mM ,pH 8.0) and 1 part each of NADP (2mM) and Glucose-6-Phosphate, solution (152 mg anhydrous/179 mg trihydrate in 10 ml of water)] changes from purple to yellow color on addition of blood hemolysate . If the hemolysate is deficient in the G6PD, the purple solution remains unchanged.

Development of yellow color, at first at the interface of colorless liquid paraffin and purple colored solution below, is the sign of initiation of reaction. At the end, the whole purple colored portion turns yellow. Normal decolorization time being 30-60 minutes, G6PD carriers (heterozygous females) require > 90 minutes. In homozygous females and males, it can be > 140 minutes (Godkar & Godkar, 2003). Due to re-oxidation, the decolorized end product can recolorize back to purple, hence reading were taken every 30 minutes. Observation was made up to 150 minutes for any possible recolorization and hence reversal of the result.

To evaluate the extent of usage of dapsone in the population under study and hence infer about the impact of possible dapsone induced hemolysis especially in G6PD deficient patients, a survey of sale pattern of the implicated drug at the institutional pharmacy store of C U Shah Medical College Hospital, Surendranagar was simultaneously undertaken over the study period.

As the sample blood was not collected solely for this experimental purpose (blood samples were drawn by laboratory for other investigations directed by physicians), individual consent from the patient was not needed as per directive of the Institutional Human Ethics Committee.

Results

Out of 150 subjects studied , 10 (i.e. 6.66%) were found G6PD deficient. In the tested 150 samples, Harijans were found to have maximum G6PD negative status – 3 females

and 4 males (total 7) out of 26 (i.e. 27%). Other communities screened negative for G6PD were *Rabari* (1 male out of 7 males and 1 female out of 9 females; in total 2 negative out of 16, i.e. 12.50%) and *Lohana* (1 male out of 2 males and out of 8 females, none was screened negative ; G6PD deficiency in 10% of them).

The samples changing color (from purple to yellow) within 30-60 minutes were termed normal in the test used. One hundred and twenty one (121) out of 140 G6PD positive subjects responded rapidly (80.66%), with purple coloration of the blood added reagent changing to yellow within 30 minutes. The remaining 19 G6PD subjects (13 males & 6 females), i.e. 12.66 % in the sample size of 150, didn't respond till 30 minutes but all these samples did so within an hour (late decolorization). They are also normal for G6PD status as per the test protocol but the importance of the delay in color change compared to the rapid decolorization in majority of subjects with normal G6PD status is unknown. In the observation period of 150 minutes in the present study there was no incidence of recolorization.

The 150 subjects were distributed in 15 communities as follows : *Bharvad* (16), *Brahmin* (04), *Darbar* (14), *Harijan* (26), *Jain* (04), *Khatri* (02), *Koli* (22), *Lohana* (10), *Luhar* (03), *Muslim* (14), *Patel* (08), *Rabari* (16), *Satwara* (05), *Sindhi* (02) and *Suthar* (04) and the G6PD

Figure 1 : Incidence of G6PD Deficiency in the visitors of CUSMC hospital, Surendranagar

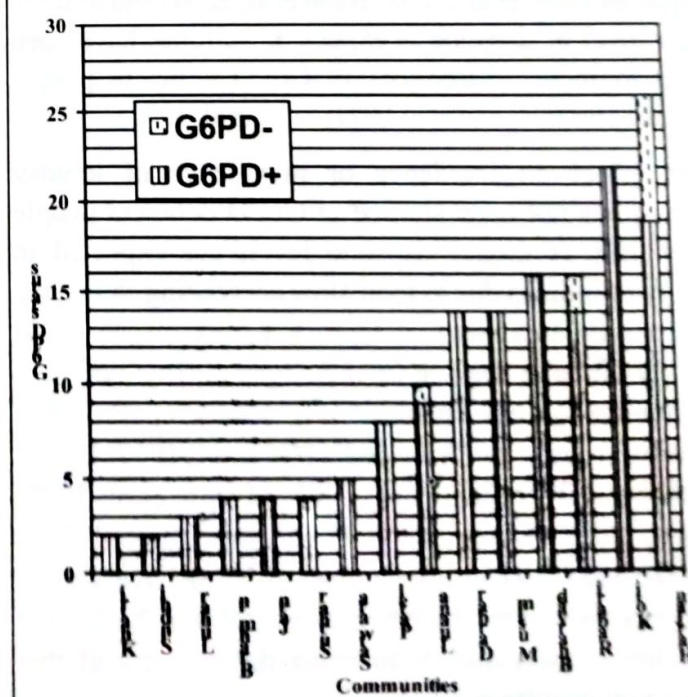


Table 3. : Labor Intervals for Patients with Vaginal Deliveries, According to Study Group.

Community	G6PD + VE (x)	G6PD -VE (y)	n (x +y)	G6PD -vity (y/n) as %	G6PD +vity x/ N (as %) (N=150)
Bharvad	16	0	16	0	10.67
Brahmin	04	0	4	0	2.67
Darbar	14	0	14	0	9.33
Harijan	19	7	26	26.92	17.33
Jain	04	0	4	0	2.67
Khatri	02	0	2	0	1.33
Koli	22	0	22	0	14.67
Lohana	9	1	10	10.00	6.67
Luhar	03	0	3	0	2.00
Muslim	14	0	14	0	9.33
Patel	08	0	8	0	5.33
Rabari	14	2	16	12.50	10.67
Satwara	05	0	5	0	3.33
Sindhi	02	0	2	0	1.33
Suthar	04	0	4	0	2.67
Total Population	140	10	-	-	6.67

status of these subjects has been reported in Table I. These findings have been portrayed in an explanatory bar chart of community-wise distribution of G6PD deficiency in Fig. 1.

Out of 150, 78 males and 62 females were normal while 6 males and 4 females were G6PD deficient. Figure II displays gender-wise distribution of G6PD deficiency. Mean age of the normal and G6PD deficient males were found to be 36.744 (=21.03) years and 36 (= 21.70) years while mean age of the normal and G6PD deficient females were found to be 34.113 (= 18.21) years and 32.75 (= 19.87). Hemoglobin levels in the normal and G6PD deficient males were found to be 12.286 (=0.84) and

11.716 (= 0.96) respectively. Hemoglobin levels in the normal and G6PD deficient females were found to be 10.523 (= 0.39) and 10.6 (= 0.28) respectively. Thus, age or hemoglobin level is not significantly different among normal and G6PD deficient persons.

Discussion

Harijans formed the largest visitor group in the hospital i.e. >1/6 (26 out of 150) and also screened for the highest incidence - 7 deficient in G6PD activity. Another 19 subjects, 6 persons (4 males and 2 females) responded after 30 minutes but within 60 minutes, endorsing normal level of G6PD as per screening procedure. Clinical significance

of the delayed positivity for G6PD is not yet known. Except *Harijan*, *Rabari* and *Lohana* subjects, none of the subjects from the remaining communities showed G6PD deficiency. *Bharvad* (16), *Darbar* (14) and *Koli* (22), if taken together, formed more than one third (34.66%) of the sample size but exhibit no G6PD deficiency.

Out of total 98,872 pieces of medicine sold in the surveyed month, dapsone selling was 1650. Two-third of Indian population being slow acetylators and out of them 6.6% being G6PD deficient, 6-7 patients (out of the 10 G6PD deficient people) are supposed to face severe hemolysis.

There is, here fore a need to the reduce the dosage of dapsone in these patients to avoid an adverse hemolysis. The prevalent mode of administration of the oxidizing drug like dapsone universally can be changed to minimize systemic side effects. For example, sulfacetamide supply from the institutional pharmacy store is limited to eye/ear drops – hardly absorbed systemically enough to induce hemolysis. Similalry, topical dapsone has also been tried without as much harm in relevant cases (Garrett, 2009).

Conclusion

To conclude, overall incidence of G6PD deficiency (6.66%) reported in this study is much above the national average of 2.5% and the incidence is especially very high among Harijans (27%) (the reason might be a study sample of mostly inbred population which has time and again shown much higher incidence of genetic diseases (Babbitt, 2006)). Thus, precautions are needed against “universal approach” of prescribing 100 mg dapsone per day for leprosy patients or even more than 100 mg for other conditions requiring dapsone. Seeing the quantum of daily dispensing of dapsone and the extent of G6PD deficiency in the population, prior screening for G6PD status and readjusting the dose of dapsone or using topical preparation for limited and localized skin involvement can reduce the incidence of haemolysis.

Seeing very few new cases of leprosy per month per institution (around 2-3 in the given case), government should plan a wider project involving statistically significant number of cases sufficient to revise a policy. The government should plan a screening of a large multi-regional population for G6PD status and evaluation of the incidence of hemolysis induced by dapsone in prospective analysis of newly registered cases of leprosy based on which, a policy revision (or revised guidelines) about prescribing and dispensing dapsone can be recommended.

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Prospective Monitoring of Adverse Drug Reactions associated with Antiplatelet and Antiepileptic Drugs in a South Indian Tertiary Care Teaching Hospital

VARUN TALLA¹, JUNY SEBASTIAN¹, RAMESH ADEPU*², MG NARAHARI¹, BS KESHA⁴, S HARSHA⁴

¹Department of Pharmacy Practice, Talla Padmavathi College of Pharmacy, Warangal

²Department of Pharmacy Practice, JSS College of Pharmacy, Mysore.

³Department of Medicine and ⁴Department of Nuerology JSS Medical College Hospital, Mysore.

ABSTRACT

A prospective monitoring of adverse drug reactions associated with antiplatelet and antiepileptic drugs was carried out in a tertiary care teaching hospital. Patients diagnosed with Acute Coronary Syndrome (ACS) or ischemic stroke receiving antiplatelet drugs (Aspirin and Clopidogrel) and epileptic patients receiving antiepileptic drugs were followed for a period of six months prospectively at a tertiary care teaching hospital. WHO probability scale and Naranjo's algorithm were applied to assess the causality of the reported ADRs, Modified Hartwig and Seigel scale was applied to assess the severity and Modified Shumock and Thornton scale was applied to assess the preventability. At the end of the study period, 15 ADR's were observed with Aspirin and 14 ADR's were observed with Clopidogrel in antiplatelet agents class and 24 ADR's with Phenytoin and 12 ADRs with Valproic acid in antiepileptic agents class. Among the antiplatelet agents, 82.75% of ADR's were found probable and 37.93% ADRs were possible. In antiepileptic drug class, 73.33% ADRs were found probable. In severity level asses in anti platelet agents, 6 ADRs were found in severity level 1 and 20 ADRs were in level 3 in severity, in anti epileptic agents 9 ADRs were in level 1 and 23 ADRs were found in severity level 2, and 15 ADR's were found preventable. Medications were discontinued in 14 cases and the dose was adjusted in 10 cases. Phenytoin and Sodium Valproate were found responsible for majority ADRs in Anti epileptic drugs class and Aspirin accounted for more number of ADRs in antiplatelet agents' class.

Key word : Adverse Drug Reactions (ADRs), Antiplatelets, Antiepileptic drugs.

Introduction

World Health Organization defines ADR as a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis, and therapy of disease, or for modification of physiological function.¹ Adverse drug reactions (ADRs) occur frequently in modern medical practice due to various predisposing factors, resulting in increasing the morbidity, mortality and cost of care. Worldwide clinically significant ADRs occur approximately in 20% of hospitalized patients and found to be the fourth leading cause of mortality.²

Patients with cardiovascular diseases and epilepsy are particularly vulnerable to ADRs due to their advanced age, polypharmacy, pathophysiology of the disease, age related changes in liver and kidney function and the influence of

heart disease on drug metabolism. The ADR potential for a particular drug varies with the individual, the disease being treated, and the extent of exposure to other drugs. Majority of significant ADRs involving cardiovascular drugs are predictable and therefore preventable.^{2,3}

Across the world, after the stroke and the dementia, epilepsy constitutes the common neurological condition seen by neurologists in elderly.⁴ In India approximately 5.5 million people are suffering from Epilepsy, among them 4.1 million patients resides in rural area and every year half million new patients are added to the existing list.⁵ The ultimate goal of the epilepsy treatment is to make the patient free from seizures without adverse effects of medication and improved quality of life. Over 80% of patients may achieve seizurefree state with one suitable

antiepileptic medication. But the remaining 20% of patients may require poly therapy for seizure control. In such situations the patients may have drug related problems such as drug interactions and Adverse Drug Reactions which will add to the economic burden.⁶ Assessing and resolving the potential drug related problems such as ADR will improve the therapeutic outcomes and also helps in decreasing the economic burden to patients.

Methods

A prospective observational study was carried out over a period of 6 months from June to December 2009 in a tertiary care teaching hospital in Mysore. All patients who visited as the out-patients and admitted as in-patients in the departments of Neurology and Medicine of JSS Hospital, Mysore with a clinical diagnosis of epilepsy, Acute Coronary Syndrome and Ischemic stroke were enrolled in to the study. The Institutional Ethical Committee of JSS College of Pharmacy, Mysore has approved the study and strict confidentiality was assured for all the collected information.

A suitably designed documentation form was used to collect the demographic details, clinical diagnosis, dose, frequency and dosage form of Anti Epileptic Drug (AED)

and antiplatelet agents, tests performed etc. During the study period, patients were followed up regularly to monitor and report suspected adverse drug reactions (ADRs) using CDSCO ADR notification form. The causality association between the drugs and the reactions were assessed using Naranjo's Algorithm⁷ and WHO probability scale⁸. Severity of the ADRs was assessed with the help of Modified Hartwig and Siegel scale⁹. Preventability of the ADRs was assessed by the modified Shumock and Thornton scale¹⁰.

Results

A total of 439 patients with a clinical diagnosis of epileptic seizures and 170 patients with a diagnosis of Acute Coronary Syndrome (ACS) and Ischemic stroke were enrolled in to the study over a period of six months. During the study period 45 ADR's were detected from epileptic patients. Patients with ACS and Ischemic Stroke had 29 ADRs. Out of 45 patients in the antiepileptic group, 23 patients were male in the age group of 8 years to 60 years and 22 patients were female patients in the age group of 11 years to 40 years. In the antiplatelet agents group 17 patients were male patients, and 12 female patients in the age group of 41 to 70 years.

Phenytoin (23 ADRs) and Valproic acid (13 ADRs) were

Table :1 Antiplatelet and antiepileptic Medications implicated in ADR

Anti epileptic Medications implicated in ADR	Number of ADRs (n=45)	Percentage (%)
Phenytoin	24	53.33
Valproic acid	12	26.66
Carbamazepine	4	8.88
Phenobarbitone	3	6.66
Divalproex sodium	1	2.22
Levetiracetam	1	2.22
Anti platelet agents implicated in ADR	Number of ADRs (n=29)	Percentage (%)
Aspirin	15	51.72
Clopidogrel	14	48.27

ADR: Adverse Drug Reaction.

the drugs responsible for more ADR's in anti epileptic drugs class and Aspirin (15 ADRs) and Clopidogrel (14 ADRs) have contributed for ADR's in antiplatelet agents' class. Details of antiepileptic medications and antiplatelet agents implicated in ADRs are presented in Table. 1.

Majority of the reported ADRs belong to level 2 of mild severity in antiepileptic class of drugs and antiplatelet agents caused ADRs belonging to level 3 of moderate severity. Majority ADRs belonging to both antiepileptic and antiplatelet classess of the medications were not preventable. Details of Severity and Preventability are presented in Table.2.

The suspected ADRs were also classified using W.H.O preferred terms. Ataxia (Carbamzapine and Phenytoin), somnolence (Divalproate Sodium, Carbamazapine,

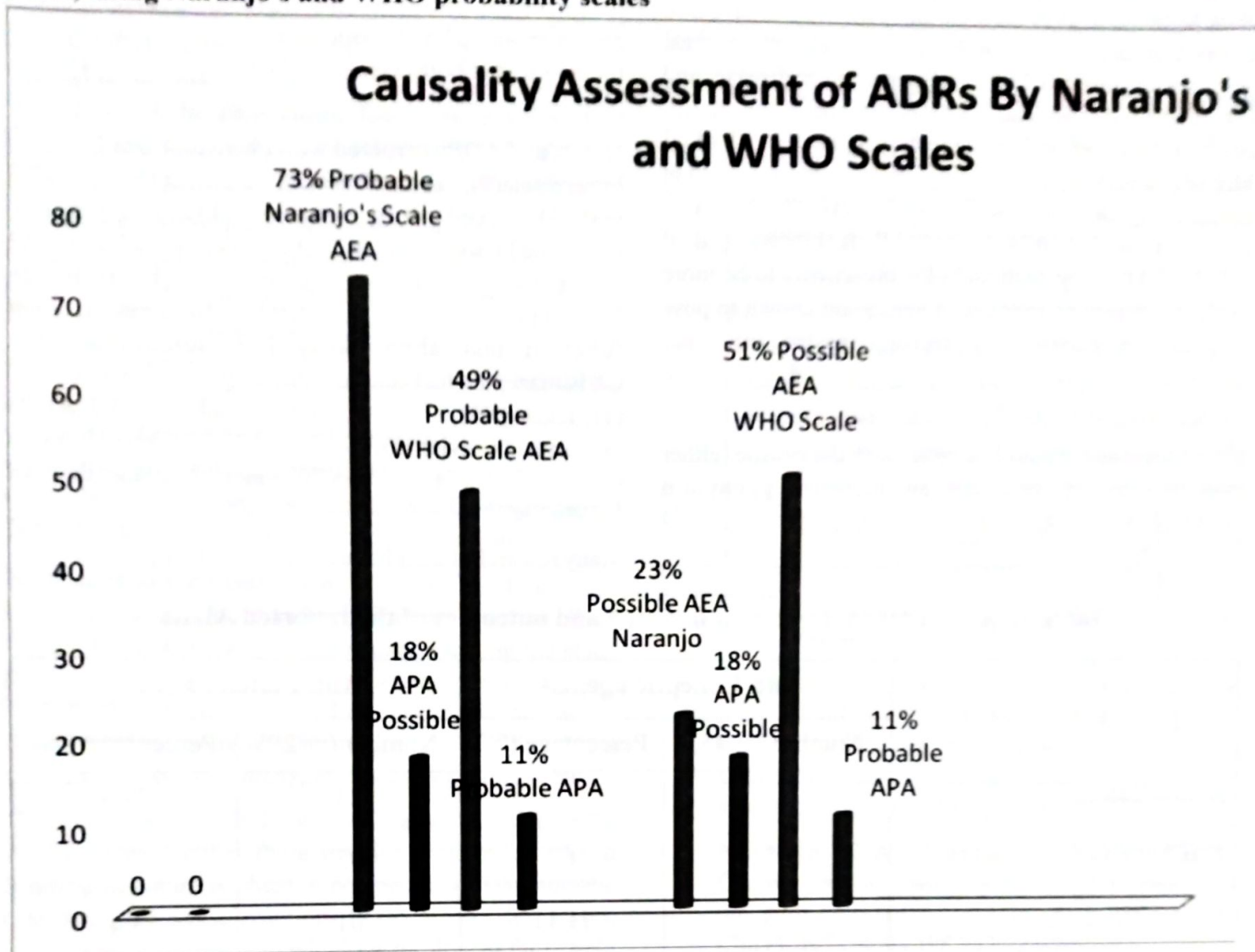
Phenytoin) dizziness (Carbamazapine, Phenytoin, Divalproate Sodium), tremors (Levitaracetam), euphoria (Phenobarbitone, Divalproate Sodium) rashes (Phenytoin, Clopidogrel), Allergic reactions (Phenobarbitone, Phenytoin), gum hyperplasia (Phenytoin), urticaria (Phenytoin and Aspirin), weight gain (Sodium Valproate), gastric ulcer (Gastric Ulcer), rash (Phenytoin, and Clopidogrel), angioedema (Clopidogrel), head ache (clopidogrel), and constipation (Clopidogrel) were the adverse drug reactions reported during the study with the antiepileptic and anti platelet agents.

A patient presented with anticonvulsant hypersensitivity syndrome with the combined use of phenytoin and phenobarbitone. Causality association between drug and reaction was found probable in 73.33% (n=33) on WHO ADR probability scale and 48.88% (n=22) on Naranjo's

Table: 2 Preventability and severity of ADRs

	Antiplatelets	Antiepileptics
PREVENTABILITY:		
Probably preventable	14	1
Not preventable	15	44
Definitely preventable	-	-
SEVERITY		
MILD		
Level 1	6	9
Level 2	-	23
MODERATE		
Level 3	20	10
Level 4(a)	2	3
Level 4(b)	1	-
SEVERE		
Level 5	-	-
Level 6	-	-
Level 7		

Figure 1: Causality assessment of ADRs of anti epileptic agents (AEA) and Anti Platelet Agents (APA) using Naranjo's and WHO probability scales



APA: Antiplatelet Agents,

AEA: Anti Epileptic Agents

scale respectively. Among antiplatelet agents, Aspirin was found responsible for 51.72% (n=15) and Clopidogrel was found responsible for 48.27% (n=14) of ADRs. Causality association between drug and reaction was probable in 62.06% (n=18) and 37.93% (n=11) as assessed by using WHO probability scale and Naranjo's algorithm respectively. Causality association of adverse drug reaction with the antiepileptic medications and antiplatelet agents using causality assessment algorithms is presented in Figure. 1.

After development of an adverse drug reaction, antiepileptic medications were discontinued in 13 cases and dose was altered in 5 cases. In antiplatelet group, medications were discontinued in one case and dose was altered in 5 cases. Symptomatic treatment was given in 33 cases for ADRs such as rash, urticaria, GI ulcer, and

abnormal behaviour and specific treatment such as use of tranexemic acid was given in 11 cases for GI bleed due to aspirin. The ADRs were continued in 38 cases (51.31%) and 26 patients (35.13%) were recovered from ADRs. The details regarding the discontinuation of the medication, symptomatic treatment and outcomes of ADRs are presented in Table.3.

Discussion

Antiplatelet agents have demonstrated effective clinical outcomes in the management of post-acute myocardial infarction (AMI), ischaemic stroke or transient ischaemic attack, and in patients with stable or unstable angina, peripheral arterial occlusive disease or atrial fibrillation and reduce the risk by 25%.¹¹ The pooled incidence rate of aspirin induced gastro intestinal hemorrhage in meta

analysis of 14 studies was found as 0.12%¹¹. In the present study, the incidence rate was found to be 0.9% which is close to the findings of the meta analysis. Studies have also shown that incidence rate will increase in elderly patients, people with previous history of peptic ulcer disease, and use of corticosteroids and NSAIDs. In one of the studies conducted by Shehab N et al mentioned that the risk of GI bleeding is very high when antiplatelet agents are given in combination as aspirin with clopidogrel.¹² The risk was estimated as 1.2:1000 in individuals receiving dual antiplatelet therapy cautioning the prescribers to be more vigilant.¹³ However antiplatelet agents are known to pose risk to the patients by causing gastro intestinal hemorrhage, skin rashes, neutropenia and cholestatic jaundice.¹⁴

Independent of the Anti Epileptic Drug use profile (either monotherapy or combination therapy) phenytoin (42.14%) was the most frequently prescribed AED followed by valproic acid (39.40%), carbamazepine

(25.05%), phenobarbitone (16.62%), clobazam (14.12%) and miscellaneous AEDs include clonazepam, levetiracetam, oxcarbazepine etc (9.69%). In antiplatelet agents group, 83.53% patients received dual antiplatelet therapy that is both Aspirin and Clopidogrel and 16.47% patients received monotherapy.

Number of ADRs involved with Phenytoin was 23 [Gum hyperplasia(9), somnolence(2), asthenia(1), ataxia(2), rash(3), fixed drug eruptions(1), dizziness(2), insomnia(1), somnolence(2)]. Valproic acid had caused 13 ADRs [weight increase (5), abnormal behavior (2), fatigue(1), menstrual disorder(1), dizziness(1), liver function test abnormality (1), somnolence(2)]. Carbamazepine had caused 4 ADRs [ataxia (2), dizziness (1), lethargy(1)]. Phenobarbitone had caused 2 ADRs [abnormal behavior (1), gum hyperplasia(1)]. Tremor was developed in one patient while increasing the dose of Levetiracetam.

Many research studies have corroborated the phenytoin is

Table 3: Action taken, treatment initiated and outcomes of the reported ADRs

	Anti Epileptic agents		Anti Platelet agents	
	Number (n=45)	Percentage (%)	Number (n=29)	Percentage (%)
Action Taken	27		23	79.3
No Change	05	60	05	17.2
Dose Altered	13	11.11	01	3.4
Discontinued		28.88		
Treatment Initiated	10	22.22	01	03.44
Specific	15	33.33	18	62.06
Symptomatic	20	44.44	10	34.48
No Treatment				
Outcome of ADR	21	46.66	17	58.60
Continued	20	44.44	06	20.70
Recovered	04	08.88	06	20.70
Un Known				

one of the causes for gingival hyperplasia.^{15,16} Despite having high incidence of gingival hyperplasia with phenytoin, patients are still recommended with phenytoin because of economic considerations. Valproic acid is reported to cause weight gain¹⁷ hepatic and renal damage, SIADH in patients. In our study, weight gain was observed in 5 patients. In such cases, the strategy adopted to decrease the weight was diet counseling and life style modifications to the patients.

The ADRs involved with Aspirin use were Urticaria (6) Gastric ulcer (8) and gastrointestinal bleeding (1) and with Clopidogrel use were Rash (4), Angioedema (2), Headache (3), and constipation (5).

Among the ADRs developed by antiepileptic agents the highly affected organ system class is Gastro intestinal disorders followed by Central peripheral nervous system disorders. Among ADR's developed by antiplatelet agents the highly affected organ system class is Gastro Intestinal Disorders followed by skin and appendages disorder.

No change in the treatment was observed in 40 cases as those ADRs were mild and self limiting in nature. Even though there was no overdose situation among the study population, 10 patients improved when dose was altered. 14 patients were discontinued of their medication as the ADRs were so severe like Gastrointestinal bleeding, Liver damage, Anticonvulsant hypersensitivity syndrome etc.

Majority of patients did not receive any treatment for the ADRs because either these reaction were mild and self limiting in nature or there is no specific or symptomatic treatment for some reactions. Also among few cases, patients were not ready to withdraw the drug as the benefit from the drug was outweighing the risk and the alternative drug was more costlier than the existing one.

Conclusion

Unlike studies done earlier, Phenytoin and Valproic acid were attributed to majority of adverse drug reactions in antiepileptic class. Aspirin attributed for majority of ADRs in antiplatelet class of medications. The organ system class effected in both groups was Gastrointestinal system and the ADRs were Gum hyperplasia, GI bleeding as well as short term ADRs like constipation.

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Pharmacovigilance Study of Some Ayurvedic Drugs in Diabetic Patients

SHOBHA KULSHRESHTHA¹, UMA ADVANI¹; RAFI MOHAMAD²

¹Department of Pharmacology, NIMS Medical College, Jaipur,

²NIMS Institute of Pharmacy, Jaipur.

ABSTRACT

Ayurvedic drugs share a big part in the life of densely populated country like India. As these drugs are of natural origin, the medical professionals earn a greater financial profit by publicly saying that such drugs are the safest with no adverse effects. But this is not true. As compared to allopathic drugs, ASU (Ayurveda Sidha & Unani) drugs are safe but still these have some potential of causing Adverse Drug Reactions (ADRs). This study was aimed to determine ADRs as a result of ayurvedic treatment and also positive side effects if any, giving the the contrubtion to pharmacovigilance of ASU drugs in India. In this study, 50 newly diagnosed patients suffering from diabetes of either sex or age were given the same combination treatment of dried gurmur, jamun seed powder, Black caraway and aloe juice in a final dosage form. The regimen as usual helped the patients in controlling their elevated blood glucose levels but it was not totally free of ADRs. In our study it was observed that a total of 148 non serious ADRs had occurred which were metallic taste (20.5%), nausea(19.8%), constipation (8.9%), flatulence (8.2%), dry mouth (7.5%), loss of libido (7.5%),throat itching(2.7%), loose stools (6.8%), bitter taste (5.5%), vomiting (4.1%), phlegm formation (2.7%), irritable bowel(1.4%), and taste disturbance(1.4%). From casualty assessment it was found that gurmur(66%), jamun seeds(14%), Black caraway (12%), and aloe (8%), were responsible for causing all the above ADRs. This study highlights due importance of pharmacovigilance of herbal drugs and need to stress due importance to avoid indiscriminate drug use.

Introduction

Herbal medicine a broad term used for herb material and herbal preparations .They are crude plant material such as leaves, flowers, fruits, seeds, stems, wood bark, roots or other parts of plants. They are used for prevention, diagnosis, treatment or improvement of symptoms of illness.

In India, the turn over for medicinal plants was estimated to be about Rs.5.5 billion per year. Though there are various approaches to reduce the ill effects of diabetes and its secondary complications, herbal formulations are preferred due to lesser side effects and low cost. A list of medicinal plants with proven antidiabetic and related beneficial effects and of herbal drugs used in treatment of diabetes is compiled (1) As with system of medicine , pharmacovigilance or safety monitoring of herbal medicines implies detection of any adverse event relating to use of medicine, assessment and communication risks

and benefits of medicines.

Traditionally, herbs and herbal products have been considered to be non- toxic and have been used by the general public and ayurvedic medical doctors world-wise to treat a range of ailments. The truth is that some herbs can be dangerous and can bring about serious adverse effects and even lead to death. (2) There are fewer pharmacovilance studies on herbal medicines than conventional drugs, mainly because unlike synthetic drugs, herbs cannot be patented, and there is little money to be made by funding and research. But herbs and herbal preparations can cause toxic adverse effects, serious allergic reactions, drug interactions and also can interfere laboratory tests. (3,4) Recent researches demonstrated that many traditionally used herbal medicines are and are even mutagenic and carcinogenic. (5 ,6,7) The number of adverse reactions of ayurvedic drugs reported to National

pharmacovigilance centre in India are negligible.

Therefore this study was done to:

Determine the prevalence of adverse effects associated with the use of some ayurvedic preparations for Diabetes mellitus.

To observe if any side effect of these drugs in Diabetes mellitus.

In ayurveda, the dried leaves of the climber 'Gurmar' (meaning "destroyer of sugar" in Hindi), *Gymnema sylvestre* (family Asclepiadaceae) has been used in India for management of diabetes for about 2000 years. The herb has shown to reduce blood sugar, glycosylated plasma proteins when used for 18-20 months. The active components responsible for lowering glucose are the gymnemic acids. Gymnemic acids are anti sweet principles and exhibit inhibitory effects on levels of plasma glucose. From extracts of leaves were isolated glycosides, Gymnemic acids, which exhibit anti-sweet activity. This effect lasts upto 2 hours (1, 8). Some postulate that the herb actually reduces craving for sugar by blocking receptors in the tongue. *Gymnema Sylvestre* may be useful as therapeutic agents for the stimulation of insulin secretion in individuals with Type 2 Diabetes. (9)

Syzygium cumini (Linn.) , member of family Myrtaceae commonly known as Jamun in Hindi and Black plum or Black berry in English , is a large size evergreen tree and possess anti - diabetic activity according to Ayurvedic system of medicine of India , *S.cumini* is being widely used to treat diabetes by the traditional practitioners over many centuries.(10,11)

The leaves are antibacterial, the fruits and seeds are used to treat diabetes, pharyngitis, splenomegaly, urethrorrhea, and ring worm infection. The leaves have also been extensively used to treat diabetes. The dose of dried powdered seed is 1-3 gram as per the Ayurvedic Pharmacopoeia of India.

Black caraway, *Carum carvi* commonly known as Kala zeera belonging to family umbelliferae has various medicinal properties (20). A poultice made from the powdered seeds is believed to be an effective herbal remedy for healing of wounds, especially in diabetes. (12, 13) The dosage of dried powdered seed is 500mg -2 gm as per the Ayurvedic Pharmacopoeia of India

Aloe vera , *Aloe barbedensis* , commonly known by saskrit word Kumaari , belonging to family Liliaceae has been

used for centuries as a medical substance. *Aloe vera* has been widely used as having a number of benefits when taken internally. *Aloe* has been marketed as a remedy for coughs , wounds, ulcers, gastritis, diabetes , cancer, headaches, arthritis, immune-system deficiencies. Preliminary studies suggest that aloe juice may help to lower blood sugar levels in people with type 2 (Maturity) diabetes and intake of aloe vera has been linked with improved blood glucose levels in diabetes and lower blood lipids in hyper lipidemic patients.(14,15) The dosage of dried leaf pulp in the powdered form is 125-500 mg as per the Ayurvedic Pharmacopoenia of India.

Material And Methods

Present study was undertaken by the department of pharmacology in NIMS Medical College &Hospital, Jaipur in collaboration with department of medicine ayurvedic research centre Indore.

Study design and population:

A clinical prospective study was conducted in total 50 patients of either sex between 18-60 year age group were enrolled for the study attending out- patient department diagnosed for diabetes mellitus.

All the patients were treated with dried powder of Gurmar 1 gm, Jamun seeds 1gm, Black caraway 500 mg and purified form of *Aloe vera* 250 mgs (Doses as per The Ayurvedic Pharmacopoenia of India , Volume I.)

Once daily orally for 2 months .Total period for the study was 6 months.

Protocol design was approved by the Institutional Ethical Committee . Informed consent was obtained from all patients enrolled for the study.

Inclusion criteria: Newly diagnosed patients of type II diabetes mellitus who were not treated with any ayurvedic or allopathic medicines earlier.

Exclusion criteria: 1.Patients suffering from any other chronic or systemic diseases.2.Pregnant and lactating women3.Patient on any other medication.

Data collection and analysis: A questionnaire form included essential medical enquiries such as patients demographic, signs and symptoms, past medical history ,laboratory findings and investigations, diagnosis, treatment, and details of adverse events, suspected drug dechallenge, rechallenge, out comes, causality assessment and score using Naranjo's Algorithm and narrative (16).

The forms were filled and completed by patient and investigator. After the diagnosis was made all patient were given oral ayurvedic combination of medicines. Follow up every 15 days interval for 6 months. If any AE observed by the patient was recorded & reported Dechallenge and rechallenge was being carried out to determine the suspected drug and its association with ADR/AE. Finally with the help of 10 questionnaire algorithm, causality assessment was done for the suspected drug and scores were noted to classify categories. (16, 17)

Results

In the above study, all patients were treated for diabetes with gurmar, jamun seeds, Black Caraway, and aloe vera in the prescribed doses, total 50 patients, 31 male and 19 female patients were enrolled for the study. At the end of the study it was observed that a total of 148 non-serious events had occurred either single or in association in all 50 diabetic patients.

None of the patient under study died / hospitalized or had caused any life threatening serious adverse event. More number of ADRs were recorded in males with 90 reports (60.8%) as compared to 58 reports (39.2%) in females. (figure 1) The highest number of ADRs that had

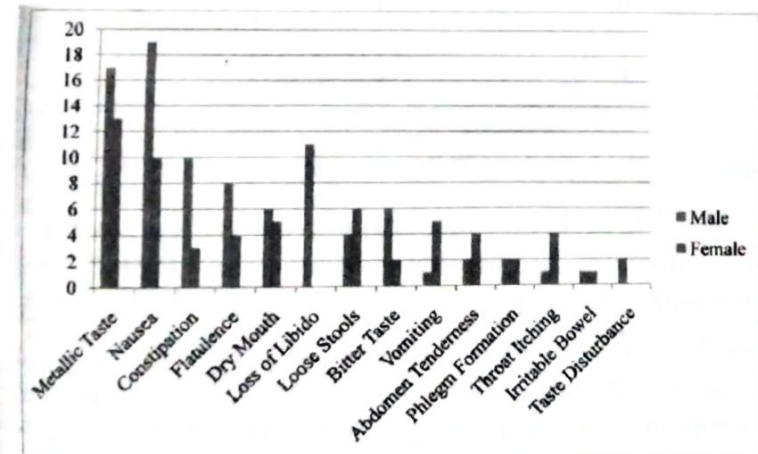


Figure 1 Bar graph representing various ADRs (x-axis) versus no. of reports (y-axis) in diabetic males and females

occurred irrespective of gender was in (51-55year) accounting for 52 reports (35%) in age group (56-60year) with 37 reports (25%) and least number of reports in (36-40year) group consisting of 10 reports (6.8%).

The maximum number of ADRs reported were metallic taste with 30 reports (20.6%), nausea, 29 reports (19.9%) and 11 reports (35%) indicating loss of libido in males out of 31 male patients exposed.

System class wise ADR are shown in (figure 2)

Dechallenge and rechallenge was done in 42 patients out of 50 patients to have causality assessment. It was found that out of 148 events, 18 (12.2%) were definite ADRs, 95 (64.2%) were probable, 11 (7.4%) possible and 24 (16.2%) were unassessable ADRs as shown in (Table 1)

Distribution of ADRs according to drugs in diabetic patients is shown in Table 2

System Organ Class wise ADR of Diabetes

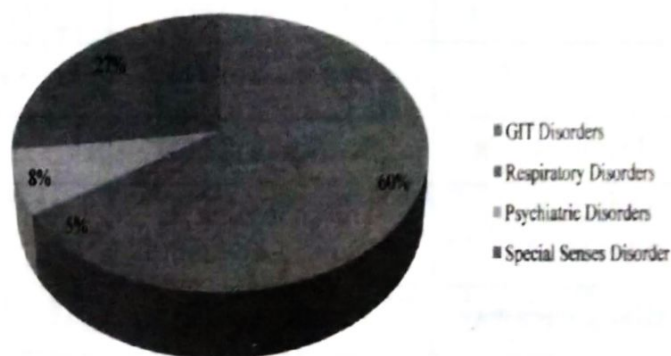


Figure 2 Distribution of ADRs according to System Organ Class (SOC) in diabetic patients

Discussion

In our study, out of 50 diabetic patients enrolled, 31 were male (62%) and 19 were female (38%). More number of ADRs reports were recorded in males in the 51-55 yrs age group (18). It may be due to under reporting by female patients.

The maximum number of ADRs were metallic taste, nausea and loss of libido in males with *Gymnema sylvestre* mild gastro entestinal disorders /upset was observed and if taken with food these effects can be minimized. None of the patients had any life threatening or serious event. No severe side effect was seen in any of the patient with these drugs under study. Dechallenge and rechallenge was done to have causality assessment and assessment was done according to Nirango's Algorithm with all the herbal drugs. The coding of all the ADRs according to WHO's ADR terminology for Indian system of medicine (19) that had occurred in the diabetic patients such as metallic taste, nausea, constipation, flatulence,

Table 1: Causality Assessment

Drugs	Events	Definite	Probable	Possible	Unassessable
Gurmar	Total (148)	18(12.2%)	95(64.2%)	11(7.4%)	24(16.2%)
	Metallic taste (30)	6	20	1	3
	Bitter taste (8)	2	4	–	2
	Taste disturbance (2)	1	1	–	–
	Loss of libido (11)	–	9	–	2
	Nausea (29)	7	20	–	2
	Vomiting (6)	1	3	1	1
	Dry mouth (11)	–	10	–	1
Jamun seeds	Constipation (13)	–	7	4	2
	Throat itching & phlegm formation (8)	–	4	1	3
Black caraway	Flatulence (12)	–	7	2	3
	Abdominal tenderness (6)	–	5	1	–
Aloe Vera	Hard stool (10)	1	6	1	2
	Irritable bowel (2)	–	1	1	–

dry mouth, loss of libido, loose stools, bitter taste, vomiting, abdominal tenderness, phlegm formation, throat itching, irritable bowel, taste disturbances. Most of the adverse reactions belonged to category “probable” based on causality assessment similar to other studies (20,21). 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 hospitals by patients.

Ayurvedic herbal drugs are preventive, curative and restorative, in the health care of man. Prolong and uneventful use of substance offers testimony of its safety.(22,23) However, investigations of the potential toxicity of naturally occurring substances widely used as ingredient in these preparations has revealed previously unsuspected potential for systemic toxicity, carcinogenicity and teratogenicity (24,25,).

TABLE 2 : Distrubtion of ADRs according to drugs in diabetic patients

SR. NO.	DRUG	ADR (%)
1.	Jamun seeds	14
2.	Gurmar	66
3.	Black caraway	12
4.	Aloe vera	8

Conclusion

Herbal medicines are of great importance to the health of individuals and communities, but their quality assurance, safety, adverse effect, profiling needs to be developed in a greater way which will not only increase the confidence of these herbal drugs to care the disease but also increase their international trade.

Such studies of focused ADR reporting and

pharmacovigilance could be very helpful in reducing morbidity/mortality as well as pharmacoeconomics (health cost) and help in rationalizing drug therapy in specific diseases and drug related scenario. Therefore continuous drug safety monitoring through pharmacovigilance is essential to safeguard against adverse effects of herbal drugs.

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Dear Sir,

This has reference to the article titled **"Pharmacovigilance of Ayurvedic Siddha and Unani Drugs and Provisions of Drugs and Cosmetics Act 1940"** published in your esteemed 'Journal of Pharmacovigilance & Drugs Safety' Vol. 8, No. 1, Jan-Mar, 2011, page 43-46.

The authors have tried to review the current regulatory requirements of Ayurvedic medicines in India and have touched the subject of pharmacovigilance very briefly. The authors could have done more justice by elaborating this important aspect in the article by reviewing prevailing international practices of pharmacovigilance of herbal drugs outside India.

We are extremely sorry to observe that the authors have used this Journal more to criticize Indian Systems of Medicines including Ayurveda/Homeopathy/Yoga/Unani and Siddha rather than providing the constructive inputs for the same. We are reproducing below few excerpts from the article.

"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 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....."

It is apparent that the authors do not have the basic understanding of the research on Indian Systems of medicine and have an issue of mindset. It is one thing to be proud of something which is borrowed from West and is available without any extra efforts but is entirely different thing to develop our own system and bring it on par to compete in the global scenario.

Authors would do yeomen service by conducting Pharmacokinetic studies on any important Ayurvedic medicinal plant like *Ashwagandha* and make positive contribution to the system rather than criticizing it for lack of data. A look at the articles published in the Indian Journal of Pharmacology over the decades would provide

the evidence of the efforts on research on these systems of medicine.

Authors of the article might be aware that Indian Systems of Medicine have suffered setbacks for thousands of years, be it Mughal period or British period but despite that if the system is still in practice and common Indian people still have trust on the system, it must be having its own strength, which have kept it alive despite onslaught of thousands of years. It is only last 2 – 3 decades when the Government of India have started encouraging R&D in this Indian Systems of Medicine.

It is an earnest request to the authors and anybody else sharing these views to submit a good research project to the Department of AYUSH/Department of Biotechnology/Indian Council of Medical Research on the subject picked up from Indian Systems of medicine and make positive contributions to the system. It is always easy to criticize anything rather than making positive contributions. The statements like **"The government of India is also supporting these systems of therapeutics which are unscientific, illogical, unreliable and not based on proper experimental work"** are highly objectionable. Authors should submit an unconditional apology to the faith keepers, practitioners and believers in Indian Systems of Medicine in India. This sentence was least expected in the reputed 'Journal of Pharmacovigilance & Drug Safety'.

You may be aware that the Founder President of this Society Prof. K.C. Singhal is also the architect of introducing a national project on pharmacovigilance of AYUSH products in India. We take it as an insult to the Founder President of our Society of which I am also the member. The authors should tender unconditional apology to the Society also.

CHANDRAKANT KATIYAR

Member Society of Pharmacovigilance, India, United States Pharmacopoeia (USP), Herbal Task Force of Department of Biotechnology, Expert Committee on 'Herbal Products and Crude Drugs', Indian Pharmacopoeia Commission, Technical Review Committee of Medicinal Plant Monographs, ICMR.

Dear Sir,

This is with reference to the above mentioned published article "Pharmacovigilance of Ayurvedic Sidha and Unani Drugs and Provisions of Drugs and Cosmetics Act 1940. J Pharmacovig Drug Safety 2011; 8 (1): 43-46. " in your esteemed journal by R K Jain and R K Arya. I would like to draw your kind attention to few of my following observations:

1.Refer Page 45, 3rd Para: "In the herbs mentioned in the books of Ayurved, Sidha 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." I would like to state in this regard that Drugs & Cosmetics Act, 1940 has given separate definitions for "Drugs" and "ASU Drugs", thus this statement is unwarranted. There is an existing separate regulatory body in India in the form of Department of AYUSH, under Ministry of Health & family welfare, Government of India.; which regulates ASU drugs in India.

2.Refer Page 45, 8th Para: "Now-a-days Ayurved, Homeopathy, Yoga, Unani and Sidha system of medicine are becoming popular in India and many other parts 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." I would like to say here that these Indian Systems of Medicines including Ayurveda are part of our law in the form of Drugs & Cosmetics Act 1940. I have myself seen many patients in my clinical experience, who have given history of getting cure / relief through Ayurveda or other Indian Systems of Medicine.

I am from modern medicine background; however I have full respect for our traditional medicines. I am in favor of establishing Pharmacovigilance systems not only for Drugs but also for ASU drugs in India; however, to me it appears that the authors of the articles are biased against officially recognized Indian Systems of Medicine (ASU drugs).

Hope you will take my comments / observations in the best interest of the journal as well as our traditional systems of Medicine.

Dr Anju Gupta
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XII Annual Conference of Society of Pharmacovigilance (India) (SOPICON - 2012)

Date : Pre-conference workshop on 23th November, 2012
Conference on 24th & 25th November, 2012

Venue : Santosh Medical College, Ghaziabad, NCR Delhi

PRIZES :

- The society offers two prizes for young scientists in the field of Pharmacovigilance :
- ♦ Uppsala prize for best paper presented in special session on Pharmacovigilance
 - ♦ Best poster award

ORATIONS:

- ♦ Prof. John Autian Oration
- ♦ Prof. K. C. Singhal Oration

Conference Secretariat:

Prof.B.R.Sainath Iyer, Organizing Secretary
Professor of Pharmacology
Santosh Medical College, Santosh Nagar,
Pratap Vihar, (U.P) 201009, Ghaziabad, NCR Delhi
Phone (M) 8447181159 & 9717949645
Phone (0) 0120 2840757
E-Mail drsainathiyer@gmail.com, sainathiyerkesarsal@yahoo.co.in

XXX Annual Meeting of Indian Academy of Neurosciences

Date : October 27th & 30th , 2012
Venue : Guru Nanak Dev University, Amritsar

Conference Secretariat:

Prof. Gurcharan Kaur, Organizing Secretary
Department of Biotechnology,
Guru Nanak Dev University
Amritsar-143005 (India)
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