ORIGINAL RESEARCH PAPER

Psychiatry

KEY WORDS: Adverse Drug Reactions, Psychiatric Medicines, Side Effects of Psychiatric Drugs, Pharmacovigilance, Prescription Drugs in Psychiatry. Adverse Events of Prescription Drugs.

A STUDY ON ADVERSE DRUG REACTIONS OF SELECTED COMMONLY USED ANTIPSYCHOTIC DRUGS USED IN GOVERNMENT SET UPS IN KERALA.

Anjana Rani — Department of Psychiatry, Govt Medical College, Thiruvananthapuram, Kerala.

Revikumar K G — Director, Kerala Institute for Drugs Studies, Rajeevam, Kavaradi Road, Pettah, Trivandrum. Kerala 695024

Veena R — Professor, College of Pharmacy, Centre For Professional and Advanced Studies Ettumannoor, Kottayam. Kerala. 686631.

ABSTRACT

Psychiatric diseases in general are chronic in nature and require medicines for a comparatively long period. Often the medications exhibit certain types of adverse effects in patients on long term use. Failure to recognize the serious type of adverse drug reactions (ADR) in time may lead to continuing risk of ADR resulting in his or her quality of life. The present study on 380 participants could identify the pattern of ADRs in five commonly prescribed psychotropic medication in Kerala population. Twelve types of mild ADRs could be noted and the percentage of them varied from 0.5 (obesity) to 15.7 (excess sleep).

INTRODUCTION AND BACKGROUND

An adverse drug reaction (ADR) is an unwanted or a harmful reaction experienced by an individual who has used a drug or drugs under normal conditions and that is suspected to be related to the medicine. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, of which the US, FDA and the WHO are members, defines an ADR as a "response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function" [Clinical Safety Data Management. 1995]

The discovery and development of modern medicines have changed the way in which diseases are managed and controlled. However, evidence continues to mount that adverse reactions are common to many medicines, old and new. In some countries, adverse drug reactions (ADRs) rank among the top 10 leading causes of mortality. The selection and use of the best, safest and low cost medicines for a given patient or patients out of the many choices available requires considerable skill and awareness of the situation.

Traditional clinical pharmacology focuses its attention on the pharmacokinetics and pharmacodynamics of drugs. Such studies involve small population of subjects, generally 6 to 25. Intensive studies are made to know about absorption, distribution, metabolism and elimination (ADME) of drugs. However, such studies tell us only very little about certain characteristics of drugs after their marketing. In a country like India where drug consumption is very high, there is a tremendous scope for research in the area of adverse drug reactions.

No medicine is 100 percentage safe for all people in all circumstances. A drug, which is pharmacologically effective, may always have some hazards. The hazard may be some times insignificant or may be acceptable in relation to the drugs' therapeutic action. There is only a limited amount of information about medicines when they are first made available in the market. All hazards cannot be known before a drug is marketed. Tests in animals or clinical trials will not reveal all the possible side effects.

The studies and research related to adverse effects of medicines helped to strengthen the laws related to medicines and pharmaceuticals in many countries. In 1937 over 100 children died in the US due to renal failure as a result of the use of sulfanilamide syrup marketed by S.E. Massengill Company. S.E. Massengill was started in 1898 by Samuel Massengill .The firm manufactured the syrup by using di-ethylene glycol (DEG) as the solvent. In response to this incident, the Food, Drug and Cosmetics Act 1938 was passed in the US. Through the Act, pre-clinical toxicity testing was made mandatory for drugs for the first time. The manufacturers were also required to gather clinical data about drug safety and submit the same to Food and Drug Administration (FDA) before marketing drugs. However, no proof of efficacy was required under the Act. The FDA had 60 days to object to the marketing of drug or else it would proceed.

Little attention was paid to the adverse reactions of drugs until the early 1950s, when it was found that Chloramphenicol could cause aplastic anemia. During the Second World War, Leopold Meyler, a Dutch physician, developed pulmonary tuberculosis. He was treated with dihydro streptomycin and para amino salicylic acid. Though the details remain still disputed, he became partially deaf, believed to be due to the use of dihydro streptomycin. The incident stimulated Leopold Meyler who was bed-ridden to collect the published reports on unwanted effects of drugs and to bring them out as a volume of 192 pages, and it was first published in Dutch in the year 1951. The name of the book was 'Schaldelijke Neven werkingen van Geneesmiddelen'. In 1952 an English translation of the volume appeared under the name, ' Side Effects of Drugs', [Meyler L. Side effects of drug. Amsterdam. Elsevier 1952]. Later several updates of the book were published.

In the 1952, the American Medical Association Council on Pharmacy and Chemistry started the first official registry of adverse drug effects with the objective of collecting data on incidents of drug-induced blood dyscrasias. The FDA itself got involved in collecting reports of ADR and sponsored hospital-oriented drug monitoring programs. John Hopkins Hospital and the Boston Collaborative Drug Surveillance program developed the use of in-hospital monitors to perform cohort studies to explore the short- term effects of drug used in hospitals. Later the University of Florida- Shands teaching hospital also initiated similar program.

In 1956, Dr.Muckter and his colleagues working for the German company, Chemie Grunenthal, synthesized a drug called 'thalidomide'. It showed considerable promise as a sleeping pill and had the great advantage of not having the serious side effects of barbiturates. The discovery of thalidomide was a new venture for the company, which had earlier been specializing in cosmetics and household products. Chemie Grunenthal started selling thalidomide in Germany in October 1957 under the name "Countergan" and in England the Distillers Company started to sell it under license as "Distaval".

In the early 1960s the world experienced the thalidomide tragedy or disaster of giving birth to thousands of deformed babies. All these unfortunate babies were called "thalidomide babies" [Lenz W 1966]. On 16 December 1961 Lancet published the first report in the British Medical Press indicating that thalidomide might be a human teratogen [Mc Bide 1984] . It was a letter by Dr.William McBride of Sydney, Australia, that was published by Lancet. Epidemiologic studies established its cause to be in utero exposure to thalidomide. The FDA in US had never permitted the marketing of thalidomide.

The US was spared of the thalidomide epidemic as new drugs take longer time to penetrate their regulatory screen. However inspired by the tragedy, the Kefauver Harris Amendments were passed in the USA to strengthen the requirements for proof of drug safety. As a result of this, extensive pre-clinical pharmacological and toxicological testing become essential before a drug could be tested in man and the data were required to be submitted to FDA in Investigational New Drug (IND) Application. Moreover the amendments required the review of all drugs approved between 1938 and 1962 to determine if they too were efficacious.

In 1962 the World Health Assembly (WHA) requested the WHO Director-General to study ways to make drugs safer. After a pilot project was carried out in the USA, an international database was established at WHO headquarters in Geneva in 1971 and moved to Uppsala, Sweden in 1978.

It has been increasingly recognized that the scope of Pharmacovigilance needs to be extended beyond the strict confines of detecting new signals of safety concerns. Globalization, consumerism, the resulting explosion in free trade and the communication across borders and increasing use of the internet have all contributed to a change in the way people access medicinal products and the information about them. The prevailing patterns of drug use within the society shall have a direct link with the Pharmacovigilance activities.

India is a country of immense proportions. Its 3287590 Sq.K.M area, about 1100 million population, 16 official languages, 35 states and union territories (of which many are larger than some of the European countries) do not lend themselves to conventional logistics. Our healthcare sector has more than 15000 hospitals, 6,24,000 beds and more than half a million doctors. Large number of medicines are produced and consumed in India, which is the fourth largest producer of pharmaceutical products in the world.

In India, in spite of the large number of patients with psychiatric ailments and the huge volume of drugs being consumed, hardly any major problem with new or old psychiatric drugs has been recognized/ reported. Some can argue that it could be due to the lack of Pharmaco-epidemiological studies. India started participating in the WHO Pharmacovigilance program many years ago. Hospitals like AIIMS, New Delhi; PGIMER, Chandigarh; CMC, Vellore; JIPMER, Pondicherry; KGMC, Lucknow, and King Edward Memorial Hospital, Mumbai, were involved in the ADR monitoring set up with the help of government support. Originally the National Pharmacovigilance center was based at All India Institute of Medical Sciences, New Delhi. Many seminars and workshops were organized in the area of Pharmacovigilance and ADR monitoring. Still monitoring of ADR is in infancy in India. The 26th Annual Meeting of National Centers participating in the WHO program of International Drug Monitoring was held in New Delhi from 8-10 December 2003.

The National Pharmacovigilance Program (NPP) of CDSCO, Govt. of India defines Side effect as " any unintended effect of a pharmaceutical product occurring at doses normally used in man which is related to the pharmacological properties of the drug"[NPP Protocol November 2004]. Often 'side effect' is used as synonymous with 'adverse reaction'. An unexpected Adverse Reaction is any adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization or expected from the characteristic of the drug.

The reporting of adverse reactions to drugs is not new and it has taken place haphazardly throughout history. However, the problem of adverse drug reactions was first addressed in the 1950s and the interest in ADRs and their monitoring have increased greatly since the association between thalidomide and the "thalidomide babies" in the early 1960s [Winfield AJ 2002].

In the early 1960s, the World Health Organization was requested to study the feasibility of various measures aimed at assuring safety of medicines in the wake of the thalidomide disaster [WHO 1966]. They were also requested to establish arrangements for 'securing prompt transmission to national health authorities of new information on serious side effects of pharmaceutical preparations'. The WHO program for International Drug Monitoring was established in 1962. An international system for monitoring adverse reactions to the drugs using information derived from national centers was subsequently initiated under the Drug Monitoring program.

All drugs have the potential to cause ADRs although most produce no ill-effects in most patients. Patient groups that are more susceptible to ADR include the following -
Elderly patients
Young and neonates
Women
Patients with impaired hepatic or renal function.
Patients taking multiple drug therapy
Atopic individuals
Persons with specific genetic variations in drug metabolism
Individuals with co-existing disease states.

Adverse Drug Reactions (ADRs) contributes to overall healthcare costs by increasing morbidity and even mortality [Holland EG 1997]. A study report of 1990s indicate that one lakh Americans die each year from ADR and 1.5 million US hospitalization in a year result from ADRs of drugs. The fatality rate is 0.32% .Yet 20- 70 % of ADRs may be preventable. ADR is the fourth leading cause of deaths in the USA after heart disease, cancer and stroke [Lazarou J 1998]. Organizations like FDA give top priority for recognition and reporting of ADRs by healthcare professionals.

The essential features of adverse drug reactions are-

i) There is some evidence that a drug is responsible for the reaction.
ii) It is unintended and occurred at normal doses used clinically.
iii) The effect of the reaction is either harmful or potentially harmful to the patient.
iv) ADRs are preventable and many healthcare professionals are in a position to identify them at an early stage.
v) Patients may not always understand the issue.
vi) They are responsible for increased healthcare costs and cause a negative impact on patient, like quality of life, future compliance and trust of healthcare professionals.

Based on the frequency of occurrence of ADR, they can be classified into groups like very common, common, uncommon, rare and very rare.

Drowsiness associated with Carbamazepine is an example of very common type of ADR. Fluid retention with Carbamazepine is an example of the common type. Diarrhea-associated Carbamazepine is an example uncommon group. Depression with Carbamazepine is an example of rare type of ADR, and Arrhythmias with Carbamazepine is an example of very rate type of ADR . [Revikumar KG Miglani BD 2015].

Aims and Objectives

1. To find out the proportion of adverse drug reactions occurring to selected five psychiatric medicines namely Risperidone, Olanzapine, Haloperidol, Sodium Valroate and Escitalopram in their normal standard doses in patients diagnosed with a psychiatric disorder.
2. To identify the various factors associated with adverse drug reactions in patients with psychiatric diseases.

Methodology

Study Setting: Psychiatry OPD and Psychiatry Ward of Govt. Medical College Hospital, Trivandrum and Kottayam and selected Community Pharmacies in Thiruvananthapuram and Kottayam districts of Kerala.

Study Design : Cross Sectional Observational Study

Study Population: Patients attending Psychiatry OPDs and are using the psychiatric medicines

Risperidone 4 mg,
Olanzapine 10 mg,
Haloperidol 5 mg,
Sodium Valroate 200 mg
Escitalopram 10 mg

A total of 360 participants meeting the criteria were selected for the study which extended a period of 20 months with effect from 2023 August.

Inclusion Criteria

- Patients who are willing to take part in the study.
- Patients of either sex in the age group of 18- 65 years
- Patients using any one of the five selected drugs in the strength specified but not using the other four drugs.
- Patients who are on the use of the drug for more than 30 days.

Exclusion Criteria

- Patients who are not willing to take part in the study.
- Patients of age less than 18 years and more than 65 years.
- Patients not using any one of the selected five drugs or who are using more than one of the five drugs under study.
- Patients who are using the drugs in lower or higher strengths than their specified strengths at a time.

RESULTS AND DISCUSSION

Table 1 Distribution of Participants Based on Age (n= 380)

Age in years	f	%
18-25	54	14.2
26-35	92	24.2
36-45	94	24.7
46-55	72	18.9
56-65	68	17.9

Table 1 shows the age group distribution of the study population..

Table 2 Distribution of Participants Based on their Education. (n= 380)

Education	f	%
Primary school	60	16
Middle school	80	21
High school	42	11
Plus two	26	6.8
Diploma	84	22
Graduate	48	12.6
Postgraduate	20	5.3
Professional	20	5.3

Table 2 shows that majority (52 %) of the participants were having Plus2 or higher education .

Table 3 Distribution of Participants Based on Occupation (n= 380)

Occupation	f	%
Daily workers	120	31.5
Government employee	16	4.2
Private employee	100	26.2
Business	40	10.5
Unemployed	24	6.3
Others including domestic workers	80	21.3

Table 3 shows the employment/ occupation details of the participants.

Table 4 Distribution of Participants Based on Marital Status (n= 380)

Marital status	f	%
Married	154	40.5
Unmarried	178	46.8
Separated	34	8.9
Widow/ widower	14	3.8

Table 4 shows the marital status of the participants.

Table 5 Distribution of Participants Based on Type of Side Effects Reported (n= 380)

No of participants not showing any side effect/ ADR (out of 12 observed) is 164.

Side effect	f	% (n= 380)
Dryness of tongue	4	1.05
Fatigue	12	3.16
Memory impairment	15	3.9
Excess sleep	60	15.7
Tremor	16	4.2
Vision impairment	3	0.8
Drooling of saliva	8	2.1
Speech problem	30	7.9
Rigidity	6	1.6
Skin problem	6	1.6
Obesity	2	0.5
Muscular changes	4	1.1

The table 5 reveals that 154 participants (n= 380), that is 43% of the study population have shown any one or more of the 12 ADR symptoms noted in the study. Among the various ADR, excess sleep was the most common ADR which was noted in 15.7% of the study population.

CONCLUSIONS

Adverse drug reactions have a very important role in health care and economics of therapy. It is very much true in the case of psychiatry treatment. Though there is only limited studies on cost of drug-related morbidity and mortality in India, reports are available from other countries.

According to one study, the annual national cost of such incidents in the USA is about $ 77 billion. Classen et al estimated that for patients with adverse drug events occurring during hospitalization, the mean cost of hospitalization was greater by $4655 than that for patients who did not experience an adverse drug event [Classen DC 1997].

In a nested case controlled study within a prospective cohort study of 4108 hospital admissions, Bates et al found 190 adverse drug events of which 60 were preventable. The cost attributed to an adverse drug event was $2595 for all adverse drug events and $4685 for preventable adverse drug events. In the UK up to 3% of deaths in hospital inpatients are believed to be due to the adverse effects of drugs and death rate is approximately 5% of those patients admitted to hospitals due to ADR [Winfield AJ 2002]. Countries like USA, Australia, Belgium, France, Germany, Ireland, New Zealand have ADR monitoring systems with active involvement of pharmacists.

Since the early 1990s adverse drug events have received significant attention from scientists and researchers in quality and patient safety [Ross SD 2001]. Studies have indicated that adverse drug events occur almost daily in medium sized hospitals and out patient centers [Gandhi TK 2003,].

The essential features of adverse drug reactions are-

vii) There is some evidence that a drug is responsible for the

reaction.

viii) It is unintended and occurred at normal doses used clinically.

ix) The effect of the reaction is either harmful or potentially harmful to the patient.

x) ADRs are preventable and many healthcare professionals are in a position to identify them at an early stage.

xi) Patients may not always understand the issue.

xii) They are responsible for increased healthcare costs and cause a negative impact on patient, like quality of life, future compliance and trust of healthcare professionals.

Healthcare professionals, including physicians, nurses and pharmacists have always tried to avoid ADRs in their patients. The pharmaceutical industry also attempts to develop drugs without or with low incidence of ADRs. Still ADRs continues to be a major and serious medical problem. Now the prevention of ADRs is given much significance. Programs that monitor ADR occurrence coupled with programs that prevent ADRs help reduce the cost of treatment as ADRs can require either hospitalization or an extension of their current hospitalization.

REFERENCES

1. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Bruke JP. 1997. Adverse drug events in hospitalized patients. Excess length of stay, extra costs and attributable mortality. J. Am. Med. Assoc. 277(4):301-306.
2. Clinical Safety Data Management-1995: Definitions and Standards for Expedited Reporting. London: European Agency for the Evaluation of Medicinal Products, Human Medicines Evaluation Unit.
3. Gawali UP, Kesari HV, Gawand KS. Adverse drug reaction profile at psychiatry Out - patient department of a tertiary care centre. Int J Basic Clin Pharm. 2017;6:2428–33
4. Gandhi TK, Weingart SN, Borus J et al .2003. Adverse drug events in ambulatory care. N. Engl. J. Med. 348: 1556-64.
5. Holland EG, De Gruy FA. 1997. Drug Induced disorder. Am. Fam. Physician. 56: 1781-1788.
6. Lazarou J, Pomeranz B, Corey PN. 1998. Incidence of adverse drug reactions in hospitalized patients: A meta- analysis of prospective studies. J. Am. Med. Assoc. 279(15):1200-1205.
7. Lenz W. 1966. Malformations caused by drugs in pregnancy. Am. J. Dis. Child. 112:99-106.
8. Mc Bide. 1984. Modern Drug use. An enquiry on Historical Principles. Lancaster : MTP Press- Kluwer. 606.
9. Patel TK, Bhabhor PH, Desai N, Shah S, Patel PB, Vatsala E, et al. Adverse drug reactions in a psychiatric department of tertiary care teaching hospital in India: Analysis of spontaneously reported cases. Asian J Psychiatr. 2015;17:42–9..
10. Revikumar K G, Miglani BD 2016. Text Book of Pharmacy Practice., Career Publications, Adverse Drug Reactions. ISBN; 978-81-88739-50-9. 2009. 350-406.
11. Ross SD. 2001. Drug related adverse events: a reader's guide to assessing literature reviews and meta-analysis. Arch. Intern. Med. 161: 1041-46.
12. Winfield AJ, Richards RME. 2002. Pharmaceutical Practice Churchill Livingstone. ISBN 0443057303 Edinburgh UK.
13. WHO. 1966. International Drug Monitoring. The Role of the Hospital (Tech Rpt Ser No 425) Geneva, Switzerland.