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Instructions to Authors
Dear Readers,

Wishing you all a very Happy and Prosperous New Year 2014.

There are a few changes in the editorial team of ijopp. I take this opportunity to thank all the outgoing team members for providing their services and support to ijopp for a period of FIVE years and welcome all the new members on the board of ijopp.

All of you would agree that appropriate use of medicines is very essential to experience their complete benefits in patients. Patients are influenced by their families, part of the world they belong to, cultures and health systems in their respective countries. Therefore, the knowledge of pharmacy practice should be supplemented with disciplines that deal with people and systems such as humanistic and social sciences. It is “Social Pharmacy” that deals with the study of medicines use from scientific and humanistic perspectives.

All the social factors that influence the use of medicines in patients such as medicine-related beliefs, regulations, policies, attitudes and behavior are given importance here.

Generally, the areas of social pharmacy research could be related to pharmaceutical services and study of social factors that influence pharmacy practice and medicine use.

Social pharmacy is not much developed in India. It is the interdisciplinary discipline that enables the pharmacy profession to act, take part and take responsibility in drug matters at a societal level and hence should be introduced and given importance in the Pharmacy curricula.

Pharmacy practice and Pharm.D faculty and students of Pharm.D should take up Social Pharmacy research.

Dr. Shobha Rani R Hiremath

Editor-in-Chief
New Clinical Trials Regulations-2013 in India & its Possible Impact on Indian Clinical Trials Framework

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ABSTRACT
Submitted: 27-08-2013 Accepted: 20-11-2013

Indian regulators recently enforced two new clinical trials regulations namely “122 DAB- Compensation in case of injury or death during clinical trial” [Drugs & Cosmetics (First Amendment) Rules, 2013] & “122 DAC, (1) Permission to conduct Clinical Trial” [Drugs & Cosmetics (Second Amendment) Rules, 2013] that promise to reform Clinical-Trials conducted in India. Clinical trial sponsors are now liable for injuries or deaths that occur during the course of a clinical trial, and will be required to compensate subjects or the subject’s family. The compensation mechanism does appear to be very comprehensive and is very strongly in favor of the volunteer who participate in the trials. The regulations insist on medical management to be provided to the volunteer for as long as required and also indicate that financial compensation should be paid to the volunteers or their nominee. The regulations also define cases which would be termed as clinical trials related injury/death. Product inefficacy has been termed as a clinical trial injury.

This paper views the recent amendments as a whole, & provides a rationale for change, and offers an interrelated set of recommendations to improve the protection of human participants and enable the amendment to operate more efficiently.

Keywords: CDSCO, Clinical trial regulations, DCGI, ethical committee, ICMR.

INTRODUCTION

New Clinical Trials Regulations Issued By ICMR And CDSCO:

Recently on 30 January 2013, & 1 February 2013 the Indian Council of Medical Research (ICMR) and the Central Drugs Standards Control Organization (CDSCO) of the Directorate General of Health Services of the Ministry of Health and Family Welfare issued two new clinical trials regulations namely

- 122 DAB- Compensation in case of injury or death during clinical trial. (Drugs & Cosmetics (First Amendment) Rules, 2013)
- 122 DAC, (1) Permission to conduct Clinical Trial (Drugs & Cosmetics (Second Amendment) Rules, 2013)

In the Drugs and Cosmetics Rules 1945, after rule 122 DAA, “122 DAB- Compensation in case of injury or death during clinical trial” & “122 DAC, (1) Permission to conduct Clinical Trial” rules have been inserted.

These two new enforcements made it mandatory for investigators and sponsors of clinical trial to address issues of serious adverse events such as death of subjects involved in trials and fixing a formula for grant of adequate compensation in such cases. Though DCGI by introducing new rules for the conduct of drug trials in India, promises to reform future of clinical trials in India, many stakeholders of clinical research sector feel that DCGI is trying to provide simple & quick answers to the concerns which were raised in the Indian Parliament and other forums regarding payment of compensation in the cases of injury or death in clinical trials in India.

“122 DAB- Compensation in case of injury or death during clinical trial.” which apply to all forms of clinical research (industry sponsored, funded by government or investigator initiated). Its new provisions are given in Table 1

In the present form amendment called “122 DAC, (1) Permission to conduct Clinical Trial” gives directives, permits the local & central licensing authority to make any changes to a trial protocol regarding the “objective, design, subject population, subject eligibility, assessments, conduct and treatment”, “if considered necessary.”

This paper views the recent amendments as a whole & attempt to crystallize problems which can arise due to its implementation & provide some recommendations to improve the protection of human participants in trial and enable the amendment to operate more efficiently.

Problem 1: Research Related Injury & Inherent Risk of Injury in Research.

When a subject is injured as a result of participation in a research study it is called as “research related injury”. As per recent amendment, “122 DAB- Compensation in case of
injury or death during clinical trial”, any injury or death of the subject occurring in clinical trial due to reasons mentioned in Table 2 shall be considered as clinical trial related injury or death and the subject or his/her nominee(s), as the case may be, are entitled for financial compensation for such injury or death:

The risks of “research related injury” depend on the treatment being studied and the health of the volunteer participating in the trial. Such injuries may range from minor harms (such as bruises due to a study procedure or vomiting due to a new drug), to major injuries (such as organ damage or temporary physical disability), to catastrophic injuries (such as permanent disability or death). Injuries can be physical, psychological/emotional, social or economic and may require only acute or emergency care, or long term medical care.

According to US FDA, a clinical trial tests the potential treatments (drug, medical device, or biologic, such as a vaccine, blood product, or gene therapy) in human volunteers to see whether they should be approved for wider use in the general population. It is not known whether the potential medical treatment offers benefit to patients until clinical research on that treatment is complete. Clinical trials offer no guarantees. On the other hand, especially in oncology trials when standard treatments fail, or none exist, clinical research trials sometimes can offer hope. In short, risk of injury is inherent in any research. It is often very difficult to separate injuries traceable to the research from those that arise from the underlying disease being studied.

In clinical studies, an adverse event consists of any unfavorable medical occurrence in a subject, whether or not expected. It can be a new or worsening symptom, or disease. It can be caused by the study or be unrelated to the study.

Problem 2: Issue of Mandatory compensation

“122 DAB- Compensation in case of injury or death during clinical trial” makes provision for mandatory compensation for the following:

- Clinical trial sponsors are now liable for injuries or deaths that occur during the course of a clinical trial, and will be required to compensate subjects or the subject's family.
- The trial sponsor will have to provide the trial subject with free “medical management” for as long as it would be required.
- Registration of ethics committees and regular monitoring of clinical trials is compulsory.
- Detailed procedures for payment of financial compensation are included.
- It states that any report of serious adverse event (SAE) (SAE of death occurring in clinical trial, after due analysis shall be forwarded by the Sponsor to Chairman of Ethics Committee and Chairman of the Expert Committee constituted by Licensing authority with a copy of the report to the licensing authority and head of the institution where trial has been conducted within ten calendar days of occurrence of SAE of death.
- The compensation guidelines has given Ethics Committees (ECs) duty of determining the degree of risk and then calculating the compensation amount to be paid for research related injuries including death.

Table 1: Highlights new provisions of “122 DAB- Compensation in case of injury or death during clinical trial.”

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<td>1</td>
<td>Clinical trial sponsors are now liable for injuries or deaths that occur during the course of a clinical trial, and will be required to compensate subjects or the subject's family.</td>
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<td>The trial sponsor will have to provide the trial subject with free “medical management” for as long as it would be required.</td>
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<td>6</td>
<td>The compensation guidelines has given Ethics Committees (ECs) duty of determining the degree of risk and then calculating the compensation amount to be paid for research related injuries including death.</td>
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Table 2: Clinical trial related injury according to “122 DAB- Compensation in case of injury or death during clinical trial”

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<td>1</td>
<td>Adverse effect of the investigational product(s).</td>
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<tr>
<td>2</td>
<td>Violation of approved protocols, scientific misconduct or negligence by the sponsor or his representative, or the investigator.</td>
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<tr>
<td>3</td>
<td>Failure of investigational product to provide intended therapeutic effect.</td>
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<tr>
<td>4</td>
<td>Use of placebo in placebo controlled trial.</td>
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<td>5</td>
<td>Adverse effects due to concomitant medication excluding standard care, necessitated as a part of approved protocol.</td>
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<td>6</td>
<td>For injury to child in-utero because of participation of parent in clinical trial.</td>
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<td>Any clinical trial procedures involved in the study.</td>
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Table 3: Adverse event terminology

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<td>1</td>
<td>Adverse event</td>
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<td>2</td>
<td>Adverse drug experience</td>
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<td>3</td>
<td>Life-threatening adverse event</td>
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<td>4</td>
<td>Life-threatening adverse drug experience</td>
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<td>5</td>
<td>Life-threatening suspected adverse reaction</td>
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<td>6</td>
<td>Serious adverse event</td>
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<tr>
<td>7</td>
<td>Serious adverse drug experience</td>
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<td>8</td>
<td>Serious suspected adverse reaction</td>
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<td>9</td>
<td>Suspected adverse reaction</td>
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<td>10</td>
<td>Unexpected adverse event</td>
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<tr>
<td>11</td>
<td>Unexpected adverse drug experience</td>
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<tr>
<td>12</td>
<td>Unexpected suspected adverse reaction</td>
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• Failure of an investigational product to provide intended therapeutic effect.
• Administration of placebo providing no therapeutic benefits.
• Adverse effects due to concomitant medications.

Clinical trials are sets of tests in medical research and drug development that generate safety and efficacy data (or more specifically, information about adverse drug reactions and adverse effects of other treatments) for health interventions (e.g., drugs, diagnostics, devices, therapy protocols). In an investigational drug, the research may or may not get the desired result. Moreover, during informed consent process, the subjects needs to be informed before enrolling in a new drug trial, that they may not get the intended effect of the drug. Compensating patients being treated with new investigational products because the product did not have its intended therapeutic effect is absurd norm.

Placebo trials are carried out in new drug studies, when there is no existing drug to compare. The placebo is not expected to provide therapeutic benefit. Compensation being provided for patients because the placebo does not have a therapeutic effect is not only absurd but shocking too.

Patients with disease are frequently prescribed multiple drug therapy, most of which are standard or routine treatment which would be given to patients regardless of whether they are research participants or not. In addition, patients take the investigational drug as part of the research protocol. Adverse events occurring due to the other concomitant medications are common and are in no way related to the research itself. Having to compensate for injury resulting from these concomitant medications is again an absurd norm.

Above three points are specifically mentioned in the existing ICMR guidelines as not being entitled to compensation but the CDSCO guidelines made it compulsory.9

Phase I trials of investigational agents for cancer are a key step in cancer drug development. The primary objective of a Phase I trial is to determine the maximum tolerated dose (MTD), administration schedule and toxicity profile of an investigational drug and it provides a suitable option for patients who have exhausted available lines of therapy, or for those patients for whom no standard therapy exists. As far as volunteers of clinical trial of cancer are concerned, almost all patients have co-morbidities and cancer-related symptoms that require administration of concomitant medications.10,11

Having to compensate for injury resulting from these concomitant medications in phase I trial on cancer patients will have disastrous effect in oncology trials.

Problem 3: Lack of Expertise of Ethics Committees (ECs) & New Challenges

At present EC members see their responsibilities limited to providing approval to research proposals submitted for review as they are ambiguous about their roles and responsibilities Ethics committees face following hurdles.

Lack of trained manpower, administrative support & necessary expertise or experience to determine the exact quantum of compensation or to decide whether fair compensation was paid, Inadequate training, space allocated for EC operations, remuneration offered to members serving on EC boards. In addition to this, there is no proper communication network between the ECs functional in the various parts of the country and the DCGI.

According to the recently introduced amendment, the issue of volunteers being compensated for loss of time/wages in case of an injury has been made mandatory, therefore the DCGI designates the EC as an important regulator of ethical research & placed very important responsibilities of determining compensation on Ethics Committees. Therefore,

• EC members will need specific policy for compensation complying with 122 DAB amendment, ICMR guidelines, Schedule Y, Association of the British Pharmaceutical Industry (ABPI) guidelines & Indian Good Clinical Practices (GCP) guidelines which would be able to make distinctions in instance of medical negligence, fraud or protocol deviations leading to injury of participants. Now it is required to set up mechanism to differentiate protocol deviation related injuries from other adverse events. A tricky situation in case of death of a volunteer during a trial can occur.
• EC members should be trained enough to find out the conditions under which the patient may suffer the injury. Source documentation, protocol compliance, standard of medical care provided to the participants during the trial will have to be looked at in detail by the EC members before they give approval.
• It is most important to make the participant aware of his rights during the trial participation in terms of compensation to avoid further problems.

Problem 4: Assessing Adverse Events

At present Ethical Committee has to deal with different issues of ethics of clinical trials as given in Table 4.12

Assessing adverse event reports & reactions can be a major burden for ethics committees and investigators, because of the high volume and ambiguous nature of such events. Currently, FDA regulations for reporting adverse events are complex, and confusing.13 The regulations need to be
simplified and should be in written format so that investigators, sponsors and ethics committees understand what constitutes an adverse event, type of event to be reported and should define the required communication and coordination channels among ethics committees and safety monitoring entities, such as data safety monitoring boards, investigators, sponsors, and regulatory agencies.

**Problem 5: DCGI Failed In Implementing Compensation Issues Addressed By Various Existing Indian Clinical Trial Laws**

Indian law for clinical trials is based on the Declaration of Helsinki, the ICH-GCP Guidelines & International Ethical Guidelines for Biomedical Research involving human subjects by Council for International Organizations of Medical Sciences (CIOMS). Indian law for clinical trials has mentioned the need for the provision of compensation to participants for research related injuries according to following legislation:

- Schedule Y of 2005 (amended)
- Indian GCP Guidelines for Clinical Trials (Clause 2.4.7)
- The ICMR Ethical Guidelines for Biomedical Research on Human participants, 2000 (Section V in General ethical Issues) and 2006 (in Chapters III and IV)

The publication of the ICMR guidelines (Yr. 2000) & and the Indian GCP guidelines (Yr. 2001) stresses on the importance of informed consent document (ICD). According to the guidelines, volunteers who suffer physical injury as a result of their participation are entitled to financial or other assistance for any temporary/permanent impairment/disability. In case of death, their dependents are entitled to material compensation. Furthermore, applications submitted to Ethics Committees for prospective studies should provide the proposed financial plan (including, if necessary, insurance) to manage adverse events and compensation for trial related injuries.

In spite of these provisions, regulators never raised any issues regarding compensation, even though several clinical trials have been approved by the DCGI, over the last 5 years. 

**DCGI & ICMR: Work in Isolation.**

SOP's for EC are formulated by collaborative efforts of the ICMR & Forum for Ethics Review Committees of Asia Pacific (FERCAP) & the revised version of Schedule Y, released by DCGI describes the roles and responsibilities of EC members & provides clarity on the regulatory responsibilities of EC functions. Both the ICMR, and DCGI, do not have any autonomy over the research reviewed and approved by the ECs in our country. The ICMR guidelines are not legislated, hence, the ECs cannot act against those who violate the prescribed guidelines. Thus, the role of the EC is merely restricted to being an advisory to research.

**Problem 6: Insurance Related Documents**

In present scenario, clinical research sponsors either apply for the product liability or clinical trial specific annual contracts with insurance agencies. In the case of multinational studies, sponsors generally prefer a global insurance cover or combination of global Master Policy plus individual local policies on a per trial/per country basis. This ensures that the client has the benefit of a harmonized and consistent insurance program. In the current system, only sponsors are generally more aware about the contracts & only insurance certificates issued by insurance providers is given along with most of the documents submitted to ECs. As a result of this, investigators and EC members are always unaware of the details of the contracts.

- At present, the insurance cover offered only to compensate a volunteer in case of any additional complications that may arise due to participation in a trial. All insurance policies very clearly exclude coverage for claims where the test drug/product fails to perform its intended purpose. Insurance companies are not contemplating deletion of this exclusion in light of the recent regulatory changes. This would have a direct impact on the sponsors/CROs and they would incur a higher financial burden. This could also lead to international sponsors not showing any more interest in the Indian Territory to conduct their clinical trials.

- Indian insurance sector should formulate insurance plan which have a rapid response and fast turnaround to coverage requests & also pays for many of the routine medical costs for participants in approved clinical trials.

- No clinical research program is the same as another. Each

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**Table 4: Different issues which ethical committee has to deal with clinical trials**

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<td>Vulnerable participants</td>
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<td>Participant recruitment procedures</td>
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<td>Risk-benefit balance</td>
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<td>Privacy and confidentiality</td>
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<td>Data safety monitoring</td>
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<td>10</td>
<td>Essential clinical trial documents</td>
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<td>11</td>
<td>Clinical trial insurance</td>
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<td>12</td>
<td>Dissemination of trial results.</td>
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1. Informed consent process
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6. Risk-benefit balance
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9. Data safety monitoring
10. Essential clinical trial documents
11. Clinical trial insurance
12. Dissemination of trial results.
client's needs should be specifically reflected in the coverage offered.

- "No fault compensation" should be offered
- Local policies should be provided in local languages.

As per amendment 122 DAC,(1) Permission to conduct Clinical Trial (Drugs & Cosmetics (Second Amendment) Rules,2013) the local authority may, “if considered necessary,” impose additional conditions regarding the “objective, design, subject population, subject eligibility, assessments, conduct and treatment of” a proposed clinical trial.3

State Food and Drugs Administration (FDA), the agency for enforcing the Food, Drug and Cosmetic Act in the state, is taking initiatives to strictly implement D&C Act and Food Safety and Standards Act (FSSA) Act in the state. If local authority mentioned in the above amendment is state FDA then on one hand it would be an additional burden imposed on under-staff state FDA and on other hand CRO will have to tackle one more bureaucratic hurdle at local level.

DISCUSSION

Clinical trials industry in India is going through the regulatory evolution phase. The Government recently notified new rules for the conduct of drug trials in India, making it mandatory for investigators and sponsors to address issues of serious adverse events such as death of subjects involved in trials and fixing a formula for grant of adequate compensation in such cases. This 'protectionist proactive' approach adopted by India is very strongly in favor of the volunteers who participate in the trials. This has caused drastic fall in clinical trials this year. Not only have the number of trial approvals in the country reduced, there has also been a significant reduction in the number of sponsoring pharmaceutical firms applying for such approvals. Trials could move out to cost comparable countries such as Malaysia and Thailand. India would lose its advantage of its own assets like large and easy-to-access population with much lower cost than in the developed world. In the last few years clinical research industry was struggling and now it would be more tough.

With stringent norms & law, drug regulatory bodies can ask questions, conduct an inquiry, and take action. Apart from that, stringent norms & law will not guarantee appropriate care and compensation. Unless India introduces a more multifaceted and interconnected system of protections, appropriate care and compensation would be far beyond the means of the researchers, their sponsors, and their institutions. Present amendment has not yet taken cognizance of issues related to the varying compensation amounts in international and national trials. Fear of compensation may hamper academic initiative in areas with no perceived marketability or economic gain. With new stringent norms, Indian drug regulators may add another set of regulatory bottle-necks which has to be resolved, as trials are reducing.

It is necessary to have a regulatory system which will ensure the welfare of a volunteer; however, there is also an urgent need to safeguard the industry from collapsing all of a sudden. Keeping the regulations in line with international standards/jurisdictions would be prudent to make it a win-win situation to all. Without this, it is quite possible that the clinical trial industry in India would not grow, it may actually see a de-growth which would definitely hurt the country’s economy itself.

Present amendment focuses largely on compensation issues rather than identifying and implementing the acceptable conditions for exposure of some individuals to risks and burdens for the benefit of society at large.15

By focusing on protocol review, subject recruitment practices, inform consent procedures & adverse event monitoring, clinical research can be carried out. By adapting universal principles of justice in principles of Indian clinical trial laws, the effective participation of oppressed population in decision-making can only promote ethical side of an Indian clinical research in Indian setting. In clinical research, as such every stakeholder should consider research participants as central players, who should be protected from any harm for which an existing norms & laws have given enough emphasis on research ethics.16

REFERENCES


HIV Co-infected Patients with HBV And HCV- A Review

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ABSTRACT

Submitted: 21-05-2013 Accepted: 30-07-2013

The prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infection with HIV is significant. Co-infection with the two viruses is not uncommon. It is well established that worldwide approximately 4 to 5 million persons are co-infected with HIV. There is a considerable variation in the prevalence of co-infection in different areas. In the treatment of HIV infection, the use of highly active antiretroviral therapy (HAART) is measured and its discovery has been one of the most useful and dramatic advances in the field of medicine. Highly active antiretroviral therapy was introduced in Malaysia in 1997 for treating HIV infection. The purpose of this study is to investigate the prevalence of HBV and HCV co-infection with HIV. The initiation of HAART for human immune deficiency virus has led an era to focus on other leading causes of morbidity such as hepatitis B and hepatitis C. We will review the evaluating effects of highly active antiretroviral therapy on HIV positive patients co-infected with HBV and HCV and find out its possible outcomes. Knowledge of the effects of various treatments as well as interaction between these viruses is the key to understanding and effectively treating these patients. Recent reviews have discussed many aspects of treatment. We summarize the advanced studies regarding to the progression of HAART including effects of co-infection with hepatitis B and C virus as well as its pharmacotherapeutic outcomes.

INTRODUCTION

Approximately 350 million people are infected with Hepatitis B virus (HBV) worldwide, and the World Health Organization (WHO) estimates that approximately 170 million people are infected with Hepatitis C virus (HCV). HBV and HCV infection account for a substantial proportion of liver diseases throughout the world. Because the two hepatotropic viruses share same modes of transmission, co-infection with the two viruses is not uncommon, especially in areas with a high prevalence of HBV infection and among people at high risk for parenteral infection. The exact number of patients infected with both HCV and HBV is unknown.5

HBV and Human Immunodeficiency Syndrome (HIV) are mostly found co-infecting a single patient because the pathogens share transmission routes. The prevalence of HBV/HIV co-infection varies by geographic region and risk factor exposure, but studies suggest that up to 10% of patients with HIV have chronic HBV co-infection.2,3

Epidemiology

Globally, there are an estimated 130 million chronic hepatitis C virus (HCV) infections, with an overall prevalence of 3%. Approximately 4 to 5 million persons are co-infected with HIV.4 Infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) are among the 10 leading causes of death from infectious disease.5 The introduction of highly active antiretroviral therapy (HAART) has led to a marked reduction of morbidity and mortality in HIV infected patients,6,7 with subsequently increased importance of co-morbidities such as chronic liver diseases.5 In HIV-HBV co-infected individuals receiving HAART, unique mutations in HBV have been defined which may directly alter pathogenesis,10 and high rates of HBV mutations conferring drug resistance have also been demonstrated.11 Studies on people co-infected with HIV-1 and HBV have been limited by small size, cross sectional design, co-infected with HCV, or selection bias of a referral clinic population, which sees more severe cases.12-16

Although most studies demonstrate increased mortality among co-infected individuals, a recent meta-analysis of over 30 studies with over 100,000 patients found no increase in mortality in co-infected patients in the pre-HAART era. Post-HAART, co-infection increased risk of overall mortality but not of AIDS-defining conditions.17

The endemcity of HBV infection is influenced primarily by the age at which most infections occur. Endemicity of infection is high in those parts of the world where almost all infections occur during the perinatal period or early in childhood (for example, Southeast Asia and sub-Saharan Africa). At least 8% of the population in these areas is chronically infected and 70–90% has serological evidence of previous HBV infection.18

The estimated worldwide prevalence of HCV infection is 2.2%. Similar to HBV, geographic differences in the endemicity of HCV infection can be described based on
regional prevalences; high (prevalence 3%) moderate (prevalence 2–2.9%), low (prevalence 1.0–1.9%), and very low (prevalence 1.0%).  

Among the estimated 40 million persons infected with HIV worldwide, an estimated 2–4 million are chronically infected with HBV and an estimated 4–5 million are chronically infected with HCV. Several factors influenced these co-infection estimates, including geographic differences in the prevalence of chronic infection by age, the efficiency of exposures that account for most transmission, and the prevalence of persons at high risk for infection.

Dual infection with HBV and HCV is not uncommon in geographic areas where a high endemic level of both infections is reported, such as Southeast-Asia and Mediterranean. Differences in infectivity between HBV, HCV and HIV have been observed in several settings. HBV and HIV are more efficiently transmitted perinatally and sexually than HCV. In the perinatal setting, maternal coinfection with HIV facilitates the transmission of HCV to newborns. Despite the infection rates in these high-risk groups, rates of infection in the general population have remained low (< 0.5% among adults aged 15–49) in several countries with large populations including China, Malaysia, and Philippines.

**Human immunodeficiency virus (HIV)**

Human immunodeficiency virus (HIV) is the worldwide disseminated causative agent of acquired immunodeficiency syndrome (AIDS). HIV is a member of the *Lentivirus* genus of *Retroviridae* family and is grouped in two types named HIV-1 and HIV-2. These viruses have a notable ability to mutate and adapt to the new conditions of human environment.

In many parts of the world, the predominant mode of transmission has always been heterosexual contact. However, the rates of HIV seen in different geographical settings vary widely as the result of a complex interplay of behavioral, biological, social and structural risks (direct determinants) and vulnerabilities (i.e. factors which may not be directly linked to the transmission of the virus, but may increase the chances of the virus spreading in a particular population). Many social and demographic factors also influence the epidemiology of HIV. This striking difference suggests that young girls are particularly susceptible to infection, through having unprotected sex with older, infected, men and perhaps due to starting sex at a very young age.

The south-east Asian epidemic has been well documented in Thailand, where HIV initially spread rapidly in the late 1980s among injecting drug users and between sex workers and their clients. The government acted quickly to set up a comprehensive prevention campaign including enforced condom use in establishments used by sex workers and a mass advertising campaign. In the past 2 decades, the human immunodeficiency virus (HIV) has rampaged across the globe leaving virtually no country untouched. Despite advances in our understanding of the social, behavioural and biological factors that directly increase the risk of HIV transmission, approximately 14,500 individuals are infected daily.

**Hepatitis B Co-Infection with HIV**

HBV is a deoxyribonucleic acid (DNA) virus. In the United States, the prevalence of chronic carriage of hepatitis B surface antigen (HBsAg) is present in less than 1% of the population. The course of hepatitis B in HIV co-infected patients is characterized by the increased prevalence of markers of active viral replication (hepatitis B e antigen [HBeAg], HBV DNA). Indeed, viral replication is even further enhanced when CD4 counts continue to decrease over time.

Throughout the world more than 350 million persons are chronically infected with HBV and approximately 33 million persons are infected with HIV. HBV is transmitted by percutaneous and mucous membrane exposures to infectious agents.
HCV infection leads to chronic hepatitis in 85% of patients, and those patients have a 20% risk of developing cirrhosis during the subsequent 2 decades. Many studies suggest that HIV disease modifies the natural history of chronic HCV infection; this leads to an accelerated course of progression from chronic active hepatitis to cirrhosis, end-stage liver disease, and death.

Risk factors associated with acquiring HCV infection include transfusion of blood and blood products and transplantation of solid organs from infected donors, illegal injection drug use, unsafe therapeutic injections, occupational exposure to blood (primarily contaminated needle sticks), birth to an infected mother, sex with an infected partner, and sex with multiple partners.

Prior to HAART, people with HIV-HCV co-infection were reported to have higher HCV viral load and accelerated hepatic fibrosis. Rates of HCV-related liver disease progression appeared to be 5±10 fold higher in people with HIV-HCV co-infection. In contrast; there was inconclusive evidence to support a role for HCV in acceleration of HIV disease progression.

A 20 year prospective study found increased risk of hepatitis/liver-related deaths despite HAART among co-infected drug users (DUs) compared to HCV-mono infected DUs, providing further support that HIV accelerates liver disease in the HAART era. Hepatic steatosis (HS), a common (40%–75%) complication of HCV monoinfection and HCV-HIV co-infection, is associated with rapid fibrosis progression, although a recent meta-analysis found that it is not necessarily more common in co-infected than HCV monoinfected patients. HS is associated with increased body mass index, diabetes, elevated ALT levels, HCV genotype 3, necro inflammation, and fibrosis.

The impact of viral hepatitis co-infection on HIV

The impact of viral hepatitis co-infection on HIV natural history remains uncertain. Some studies have suggested poorer outcomes in co-infected patients. HBV infections acquired at young ages are more likely to progress to chronic infections, resulting in a high prevalence of chronic HBV infection among the general population of adolescents and adults at risk for sexually-acquired HIV. Sexual (and injection drug use) exposures account for most HBV and HIV infections in developed countries, but among HIV-positive persons in some risk groups, the prevalence of chronic HBV infection may be 10-fold higher than the background prevalence.

Understanding of HBV and HCV co-infection with HIV is particularly important in Asian countries due to high background HBV and HCV prevalence and the significant
role injecting drug use plays in transmission of HIV in the region. The interactions between HIV, HBV and HCV have now extended from the epidemiological, where partially overlapping modes of transmission and bi-directional impacts on natural history are features, to the therapeutic domain. The impact of HIV therapies on both HBV and HCV co-infection is seen through the duplicate antiviral action of some therapeutic agents, against both HIV and HBV, the impacts of immune function restoration on the natural history of underlying HBV and HCV, and the increasing issue of hepatotoxicity.

Differences in infectivity between HBV, HCV and HIV have been observed in several settings. As indicated above, HBV and HIV are more efficiently transmitted parentally and sexually than HCV. In the perinatal setting, maternal co-infection with HIV facilitates the transmission of HCV to newborns.

Pharmacotherapeutic Outcomes

Treatment of hepatitis B in an HIV-infected patient should be considered upon initial diagnosis of hepatitis B. For assessing disease activity and possible indications for HVB therapy, a quantitative determination of HBV DNA and of liver transaminases is recommended. Serum HBV DNA levels are associated with a linear increased risk for development of liver cirrhosis and hepatocellular carcinoma.

The management of chronic HBV disease in HIV infected patients is complex due to the dynamic nature of the disease, drug toxicities, antiviral resistance, potential for hepatitis flares, and the paucity of data regarding treatment of this subpopulation of patients.

As of 1989, all HCV testing was performed using ELISA, followed by confirmatory testing of positive samples with recombinant immunoblot assay (RIBAs). Although there have been several case reports of the impact of HAART on HIV-HBV co-infection, relatively few studies have specifically examined this issue. A recent Dutch study that retrospectively assessed rates of hepatotoxicity following initiation of HAART, also reported on the impact of HAART on HIV-HBV co-infection.

The timing of initiation of HAART in relation to anti-HCV therapy in co-infected patients poses challenges for clinicians. HAART may slow liver disease progression and might therefore be initiated earlier in co-infected than HIV mono-infected patients. On the other hand, HAART might increase fibrosis in co-infected patients through cumulative hepatotoxicity. Treatment of chronic HCV in co-infected individuals is a priority because of their more rapid progression to ESLD, poor tolerance of ART, and greater risk of hepatotoxicity.

There are no guidelines for the clinical management and treatment of co-infected children, and the limited experience in their management and lack of evidence base to guide policy is a barrier to achieving optimal care.

Implication of HAART in Malaysia

Since the first few cases of HIV infection were detected in Malaysia in 1986, the rate of new HIV infections reported annually has increased exponentially. At the end of 2008, there were 84,630 reported cases of HIV infections and 14,576 reported cases of AIDS. WHO, newly reported cases of HIV in Malaysia have been declining from the peak of 6,978 cases in 2002 to 3,692 cases in 2008. Since 1997, infections among women in Malaysia are up by 11% and 75% of these patients are between the ages 20 to 39. 60% of these women are married.

The discovery of antiretroviral therapy has been one of the most dramatic advances in the history of medicine. The introduction of the first nucleoside reverse transcriptase inhibitor (NRTI), zidovudine, in the late 1980s marked the
first therapeutic advances in the field of human immunodeficiency virus (HIV) infection. This was supported by randomized controlled trials (RCTs) documenting prolonged survival.11

In Malaysia, HAART can be accessed through the medical clinics of all general hospitals and some district hospitals (i.e., those with specialist physicians). Some local university hospitals also provide ARV treatment. All HIV clinics are run by specialist physicians, who have had some training in HIV medicine, and are supported by nurse counselors, who have undergone attachments at the Infectious Diseases Clinic in Hospital Kuala Lumpur. The frequency of these clinics varies from once in 2 weeks to every day.12

ART was first made available in Malaysia in 1989 and since then much effort has been put in to ensure its availability to the population via infectious diseases clinics in major hospitals and primary health clinics with family medicine physicians trained in HIV medicine. In 2006, the Malaysian government made nationwide two significant initiatives, namely the Methadone Maintenance Therapy (MMT) and the Needle Syringe Exchange Program (NSEP) targeted at intravenous drug users in an effort to encourage the use of clean sterile syringes and needles to feed their habits. In the same year, first-line ART without cost was made available for all eligible HIV infected citizens. These initiatives are starting to bear beneficial effects of treatment and the rate of HIV infection amongst intravenous drug users has declined.13

In 2006, antiretroviral drugs available in Malaysia were of three categories namely NRTI, NNRTI and PI. The list of drugs are as follows: NRTI (zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC) and AZT þ 3TC), NNRTI (efavirenz and nevirapine) and PI (indinavir, ritonavir, saquinavir, lopinavir and nelfinavir).14

Advances in ART therapy have changed the course of HIV infection. What used to be a disease with early morbidity and mortality is now a chronic manageable disease. Benefits of HAART have been reported in many western countries. HAART superiority was again proven in the present study in terms of a reduction in mortality and ADEs.15-19

DISCUSSION

Advances in ART therapy have changed the course of HIV infection. HAART superiority was again proven in the present study in terms of a reduction in mortality and ADEs.20-24 Choice of HAART regimen did not seem to be influenced by hepatitis status. Immunological and virological responses to antiretroviral treatment were similar among patients with and without hepatitis, and hepatitis co-infection status had no independent effect on survival. Co-infection with HBV or HCV, however, was independently associated with elevated ALT levels in patients on HAART. Estimated prevalence of HBV is high in the Asia-Pacific region, with at least 8% of the population chronically infected and 70–90% having serological evidence of previous HBV infection.25

The prevalence of HIV and hepatitis co-infection depends on several factors, including geographic location and background population HBV and HCV prevalence, age and distribution of HIV and hepatitis risk-exposure categories.26 The assessment of mortality using death certificates is generally well accepted. However, liver disease may have been overshadowed by AIDS-related diagnoses and not been included. For example, hepatocellular cancer was diagnosed in less than 1% of patients, thus under diagnosis is a distinct possibility. In addition, there may be differences in the assessment of the type of liver disease on death certificates.

Recently, high hepatic mortality rates in HIV/HBV co-infected patients were studied in the MACS cohort; co-infected patients were eight times more likely to die of liver disease as compared with HIV infection alone.27

Mortality due to end-stage liver disease occurred in patients with HCV infection, although other cofactors, such as alcohol use, chronic HBV infection, and use of hepatotoxic medications, may have played a contributory role in either progression or decompensation of chronic liver disease.28

However, a recent prospective study of hepatotoxicity in HIV-positive patients who were receiving antiretroviral therapy found that 88% of patients who had concomitant chronic HCV or HBV infection tolerated their medications without serious adverse effects as evidenced by liver function tests.29

Hepatotoxicity was clearly a limiting factor in the use of HAART in this cohort. The likelihood of drug-related toxicities is increased by underlying viral hepatitis. Co-infected patients should have careful assessment of possible underlying liver disease and a close laboratory evaluation when starting HAART, because abnormal transaminase levels and hepatic decompensation during antiretroviral therapy have been reported in the literature.30-32

CONCLUSION

HIV-infected patients should be monitored regularly for HBV/HCV co-infection. More aggressive and early treatment is required for the co-infected patients with high progression rates of AIDS. Initiation of HAART should be implicated before anti-HCV therapy but treatment of HBV infection should always be closely coordinated with HIV therapy.

Co-infection with HIV alters the natural history of chronic hepatitis B with faster progression to liver cirrhosis. Toxicity from antiretroviral medications explains an increased
frequency of hepatitis from HAART has been reported in individuals with HBV or HCV infection.

**Future Suggestions**

- Emerging data on development of resistance focuses the need for combination therapy instead of monotherapy.
- Patients should be monitored to detect antiviral resistance and reactivation of HBV.
- Additional research is needed to better understand the interaction of these viruses and identify better correlates of disease progression and treatment responses.

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Produce Pharmacists with Initial Professional Glow and Shine – A Call to Academe

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Hospital and Pharmacy Practices: Many people right from lay common man to medical and healthcare fraternity are not aware that the health and medical care system is incomplete without “pharmacy practice' service. The issues like prescription and medication analysis, prescription audit, rational use of drugs (RUD), patient counseling for simplifying medication regimen and to reinforce the regimen and to allay any apprehension on any possible side effects that could be anticipated and prescription economics and discussion on prescription with co-professionals is somehow not palatable to our medical fraternity or it could be also that we pharmacists have failed to grow competently to support the clinicians and also to induce confidence in them that we pharmacists are of some worth. Yet, it goes without saying that 'pharmacy practice' provides checks and balances to ensure patient's safety.

Nevertheless the doctors and patients (Hospital guests) particularly who have returned from abroad with the taste of professional pharmacy service do feel the need for such a service support for them.

So to say, the health land of India is very fertile and potential for the development and growth of 'pharmacy practice' services.

But, we need to watch out that Pharmacists we turn out from the academia are good enough with built-in quality that could match professional medical and health care system desired.

To know what should be the quality of the pharmacist, we should understand and analyze the terminal service scenario.

Pharmacy Practices: This is one of the important supportive services in a modern therapeutic practice. It encompasses logistic support, and clinical support to the clinicians and other terminal service providers. This is a subject that needs to be learnt on-site in the hospital healthcare environment. Pharmacy practice has three main streams: Logistic support service, Clinical support system, Clinical trial support service. The 'pharmacist' with his own specialization is a common fulcrum and driving force to drive the system of pharmacy practice in the healthcare scenario. To understand the pharmacy practice per se, we should first understand the 'pharmacist', his scope and limitations, the hospital service system, the scope and responsibilities of 'co-professionals' in the hospitals. Understanding these parameters is of paramount importance to the 'pharmacist' so that he can gel with the system and with the people in the healthcare system comfortably.

Hospital: In author's point of view, the hospital is:

I. An institution that provides solace to the sick
ii. A right place to render dedicated service
iii. A place that teaches and demonstrates the reality of life
iv. A place that educates the people on healthy life style
v. An indicator to the effectiveness of the preventive health care measures

In short, 'Hospital is and should be an embodiment of hospitality' this will ensue only when we consider the sick not as patient but as our 'Guest' to be treated with good hospitality.

Pharmacist: A pharmacist is a professional service provider to support the healthcare service system. He is a solution provider to various logistics and healthcare challenges. There are various streams available to the pharmacist to serve:

I. Hospital & Community pharmacist: For Logistic service, Clinical support service, Clinical trial service
ii. Industrial pharmacist: For manufacturing service, quality control service, quality audit service, clinical trial service, marketing service etc
iii. Regulatory pharmacist: For service meant for regulating import, manufacturing, movement and maintenance of standards there on under D&C and other allied Acts and Rules keeping in view the need to promote professionalism with a good understanding of the scope and objective of the pharmacy services.
It is needless to say that laxity being shown to enforce Section 42 of Pharmacy Act 1940 by the regulatory pharmacist should stop forthwith.

iv. Academic Pharmacist: In support of all the above systems and services objectively, it is again needless to say that academy should change its style of teaching and training from class room to onsite. Hence, it is the duty of the academia to give specific well oriented training on these lines to the students.

'Pharmacist' in the hospital: First and foremost quality required in a 'pharmacist' to serve in a hospital is a mindset to serve with dedication, good vocabulary for verbal and written communication skill. Pharmacist with no or poor communication skills cannot succeed. Both teachers and students should understand that 'Talking is the working tool' of a 'pharmacist'. Group discussions, active participation and presentations in meetings, seminars and workshops on semi-curricular topics with and without home-work are the tools and opportunities to train one-self to learn good communication skills.

'Pharmacist - An alien'! – A biggest challenge:

There is a good understanding among all the professionals with respect to their knowledge, scope and skills except the pharmacist as hospital is a common learning platform to all of them. Unfortunately, pharmacists' does not have such an advantage as they study elsewhere outside the hospital environment.

It is a big challenge to every 'pharmacist' to establish his position and project his knowledge and skills in the hospital system.

Pharmacy students should be taught to respect the knowledge and skills of other professionals to work and serve with team spirit. The hospital/clinical professionals look at the pharmacist to know what and how they can contribute and its value addition to the existing hospital and clinical service system. The students and the professional pharmacist should be made to understand that they are entering a service area where their duty is first to understand the existing system and other professionals and slowly bring about reforms if any needed, without disturbing the objectives and service system.

A degree may fetch a job but cannot sustain the job or fetch identity and recognition, unless there is reliable, useful professional knowledge delivered skillfully. Hence, the responsibility of the academia is paramount in bringing out pharmacist’s with built-in professionalism. Then only it is possible to fully utilize and exploit the minimum opportunity available out of legal compulsion and administrative obligation.

Practice of data sourcing and analysis:

Besides studying sourcing of drug information, the 'pharmacy practice' students should also be taught to study, understand, interpret and use:

a. Demography of the surrounding society
b. Epidemiology of commonly prevailing diseases
c. Out-patient and in-patient census
d. Disease statistics and classifications
e. Brief knowledge of identified diseases under National Healthcare programs
f. Facilities and services available

- This will help them to
  i. Prepare Standard Treatment Guidelines, Essential Drugs List, Formulary
  ii. Understand the preventive and curative drugs essentially needed
  iii. Study the drug profile
  iv. Draft drug specification
  v. Organize good logistics and clinical support

- Students should also be trained in sourcing and drafting of information for both verbal and written communication.

Drugs Logistics:

The common area where opportunities are available for pharmacist is 'Hospital Drug Logistic', a very important back up service to the healthcare service system. This involves addressing issues from the point of identifying and defining the needs to the point of use and disposal with due accountability and periodical updating to ensure free flow of funds and materials.

A good drug logistics system addresses all the issues like money, materials and stakeholders, safeguarding quality parameters associated with good time management obviating scarcity and loss.

Further, a good logistics combined with RUDs may lead to an ideal situation popularly now being called 'Pharmaco-economics' i.e.: "More output from least possible input”.

Clinical Pharmacy:

This is again a clinical support system to the clinicians provided by the pharmacists specialized in clinical pharmacy to ensure:

A. Total Quality Management (TQM) in therapy that helps in:

I. Preventing preventable medication errors
ii. Providing updated drug information to the clinicians
iii. Promoting rational therapy
iv. Good documentation of therapy
v. Helping the patients in optimizing their therapeutic efficacy
vi. Counseling the patients to avoid misuse and abuse of drugs

**B. Pharmaco-vigilance:** It is a very sensitive service area where the pharmacist has to work very carefully.

The Govt. of India has given a very big impetus to pharmaco-vigilance program (PvP). It is one of the national programs under Indian Pharmacopoeia Commission and about 90 centers have been identified for the purpose. The reporting and monitoring has been simplified through user friendly software. But this program is likely to face major difficulties, attrition, and exodus and consequently stunt the progress for three reasons; 1. The 'Pharmacy practice department' the basic foundation for Pharmacovigilance program has not been established in all ADR centers and 2. No pay scale and promotional ladder have been assigned to the cadre of pharmacists appointed and coverage of ADRs monitored under Right to Information (RTI) and consequent use of information on the subjects concerned with ADR being not addressed.

Here again, the attitude, approach, way of talking/written communication of the pharmacist – all play a major role in motivating and mobilizing the information.

Any adverse comment could disturb the patient-hospital relationship, patient–doctor/staff relationship. It is not only counter productive but may also boomerang and deprives the pharmacist from getting into this sensitive clinical area.

**C. Pharmacist in allied services:** Opportunities to serve in unconventional and not so common situations would be available in the hospital service system. Pharmacists should explore to identify themselves in 'disaster management', 'emergency services' and 'de-addiction programs' conspicuously.

Pharmacist should have a good understanding of the various health problems that occurs typically consequent to the disasters and drugs required to support medical team attending the victims.

Study of the cases being brought by ambulance will help in developing small kits commonly required for use on such patients. Students should be taught to prepare kits for various types of disasters.

**Since not much attention is given to this need in the hospital, pharmacist can definitely score a point here.**

Innovative services are the ones that would fetch good recognition, status and identity. The innovative creativity could be an altogether new service, a value addition to the existing services. Students should be motivated to study the existing system and develop any possible innovative improvement. Example: Tracking movement of antimalarial drugs may lead to identify malaria prone areas much earlier to healthcare filed staff.

**Preparing for service:**

**SWOT analysis:**

- Assessing ones Strength, Weakness against Opportunities available and Threats one would face is a good way of self analysis (SWOT analysis).
- SWOT analysis should be explained and the students should be asked to do SWOT analysis on themselves.
- This exercise will make them understand their weakness and limitations and helps them to develop their strategy with knowledge, skill and personality to face and to overcome the challenges ahead.
- Professional pride is acceptable but egoistic attitude is an enemy to the profession not acceptable anywhere. Academia should desist from ego boosting lessons, speeches and advices to the students. On the other hand, students should be taught to respect the knowledge, skill and service of co-professionals.

**Professional approach:** The next step is self presentation as an acceptable professional with a good professional dress code, personal hygiene with positive attitude free from bad, unhealthy habits like smoking, chewing tobacco etc.

**Such professional culture should be inculcated right at the student level.**

In Conclusion, the future of pharmacy service sector is in the hands of the academia. Academia should seriously introspect and impart field oriented onsite education. Producing pharmacists with initial professional glow and shine is the only way and the best way to facilitate them to have a good respectable footing in the hospital right from the day one of their career.
INTRODUCTION

Post-operative pain is multifactorial. Apart from the surgical trauma to the abdominal wall, visceral pain or deep intra-abdominal pain accounts for a significant amount of discomfort during the post-operative period, more so in laparoscopic surgery. Muscle spasm is also a common cause of pain in the postoperative period. This pain probably results partially from the direct effect of muscle spasms in stimulating mechanosensitive pain receptors. The indirect effect of muscle spasm also compresses the blood vessels and cause ischemia. Thus pain and smooth muscle spasm sets in a vicious cycle. Involved in the vicious cycle is the arachidonic acid cascade, which leads to the formation of prostaglandins, which are the important mediators of spasmogenic response of smooth muscles. Inhibition of cascade is therefore important to the control of spasm and pain.

Antispasmodic agents relieve the spasm of smooth muscles and there by pain. Drotaverine Hydrochloride is a well established directly acting, smooth muscle anti-spasmodic that brings about quick and effective pain relief by inhibiting enzyme phosphodiesterase IV and calmodulin. It is devoid of any anticholinergic side effects. To counter the pain component unrelated to spasm or secondary spasm where several inflammatory mediators are involved, the Non-Steroidal Anti-Inflammatory Drugs (NSAID's) provide relief. A combination of Drotaverine with an effective and relatively longer acting NSAID which has established safety and no interaction with Drotaverine would be an effective therapeutic strategy for sustained pain relief. The choice of NSAIDs in clinical practice mostly depends on their analgesic potencies, the adverse effect profile, and their cost. Aceclofenac is a novel, long acting, well tolerated NSAID with lower incidence of side effects and established safety profile which provides sustained pain relief by preferentially blocking COX (Cyclo-oxygenase) II enzyme, making it an ideal NSAID for combining with fast acting Drotaverine, for effective pain relief from post-operative procedures. The relative efficacies of the two drugs are therefore complimentary for effective pain relief as has been shown in previous trials. The aim of the present study is to compare the efficacy of pain relief and adverse effects profile of a single NSAID drug (Aceclofenac) versus a combination of the same NSAID combined with a potent antispasmodic (Drotaverine) in patients undergoing laparoscopic procedures involving hollow visceral organs.

MATERIALS AND METHODS

The Ethics Committee of Sir Gangaram Hospital (IRB) approved this open-label, randomized clinical trial. The trial was conducted in accordance with the ethical standards on human experimentation as per the Helsinki declaration of 1975 (revised in 1983). The study was registered in the Clinical Trial Registry of India (CTRI) before undertaking the trial.
Both male and female patients between 18 and 60 years of age admitted for laparoscopic surgeries of hollow visceral organs not necessitating restriction of oral feeds were recruited. Because both the drugs had to be given orally, procedures needing bowel resection or extensive bowel handling were excluded from this study that would have precluded early resumption of feeding. The exclusion criteria are mentioned in Table I. Randomization was done by a computer-generated sequence, with the help of the software www.randomization.com, and stored in sealed opaque envelopes.

Table I: Exclusion criteria

<table>
<thead>
<tr>
<th>No.</th>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>1.</td>
<td>Any open abdominal surgery where oral intake is not allowed.</td>
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<tr>
<td>2.</td>
<td>Patients having peptic ulcer disease/ bleeding disorders/hepatic and renal dysfunctions.</td>
</tr>
<tr>
<td>3.</td>
<td>Known hypersensitivity to any one of the active ingredients/excipients</td>
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<tr>
<td>4.</td>
<td>Any active cancer</td>
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<tr>
<td>5.</td>
<td>Chronic diseases or recent CV events (diabetes mellitus/hypertension)</td>
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<tr>
<td>6.</td>
<td>Psychotic disorders, dementia, mental retardation (Suspects who are not weakly and mentally able to personally consent for participating in this study are not eligible).</td>
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After detailed explanation of the study and involved procedures to the patients, a written informed consent was obtained. Subsequently, the patients were randomly allocated to the two treatment regimens according to their enrolled case numbers. The patients received either 100 mg of aceclofenac in combination with 80 mg of drotaverine (Group 1) or 100 mg of aceclofenac (Group 2) per os (p.o.) by random allocation. The recommended adult dose of aceclofenac is 200 mg daily taken as two separate 100 mg doses and that of drotaverine is 40 to 80 mg up to three times daily. There are no reported drug interactions between the two and are available as fixed dose combination. The pain intensity scores (VAS scores) of the patients in both the groups were recorded as per visual analog scale (VAS) (Fig. 1) by direct questioning the patients at 24 hours (Day 1), on day 3 and day 5 post-operatively. Rescue analgesics were offered as concomitant medications if insufficient analgesia was achieved.

The outcomes of the patients and any adverse events to the treatment were also noted. A Global Assessment Score was calculated and tabulated. Score 0, 1, 2, 3 was given to the response: 'Not Effective', 'Mild Effective', 'Moderately Effective' and 'Very Effective' respectively. General Evaluation, based on the clinical assessment by the Doctor was given score 0, 1 and 2 as per the following states: Worse, Same and Improved, respectively.

Statistical analysis was performed by the SPSS program for Windows, version 17.0. Data was checked for normality before statistical analysis using ShaiproWilk test. Continuous variables are presented as mean ± Standard Deviation (SD) or Median Interquartile Range (IQR) if the data is non-normal, and categorical variables are presented as absolute numbers and percentage. The comparison of normally distributed continuous variables between the groups was performed using Student's t test to compare their relative efficacies. Nominal categorical data between the groups were compared using Chi-square test as appropriate. Non-normal distribution continuous variables were compared using Man Whitney U test and for all statistical tests, a p value less than 0.05 was taken to indicate a significant difference. A Sample size of 70 per group was calculated based on a difference of 1 in patients' VAS scores between groups, a population variance of (2)², a two-sided α of 0.05, and a power of 80%.

RESULTS

A total of 140 patients who underwent laparoscopic procedures including cholecystectomy, appendicectomy, nephrolithotomy or ureterolithotomy were randomized into two groups i.e. Group 1 & Group 2. There were no drop outs till the completion of the study. The groups were comparable with respect to age and sex (Table 2, Table 3). Rescue analgesics were not given to any of the patient in either of the group.

Following the administration of the drugs there was gradual reduction in VAS scores in both the groups, however the median VAS score was significantly low in Group 1 (P<0.05) on Day 1, Day 3 and Day 5 as compared to Group 2 (Fig. 1).

Although the median VAS scores in the two groups were 3, 2 and 1 in Group 1 and 3, 2 and 2 in Group 2, the Inter Quartile Range resulted in significant difference in VAS scores in the two groups. Adverse events like nausea, vomiting, dizziness and diarrhoea were reported in both the groups however, their occurrence was significantly higher in group 2 (P<0.05), as compared to Group 1 (Fig. 2). The scores for Global assessment scores and General evaluation by Doctor were significantly higher (P<0.05) in Group 1 than Group 2 (Fig 3).
DISCUSSION

Drotaverine hydrochloride, an isoquinoline derivative, is a potent spasmytic drug which acts directly on the smooth muscles by inhibiting phosphodiesterase IV enzyme & Calmodulin. It is devoid of any anticholinergic side effects unlike other available spasmyotics like dicyclomine. Because of this anti-spasmodic action, it is widely used in biliary, renal and ureteric colic, for augmentation of labor, dysmenorrhea, and before instrumental diagnostic procedures. Onset of pain relief is observed in 12 minutes when Drotaverine is administered orally. It can be safely co-administered with other drugs and provide comprehensive pain relief when combined with analgesic and anti-inflammatory drugs. Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase (COX), preferentially COX II which is involved in the production of prostaglandins. It has superior anti-inflammatory properties and an improved safety profile than conventional NSAIDs with respect to adverse effects on gastrointestinal and cardiovascular system.

Combination of NSAIDs and antispasmodics is a promising approach to relieve post-operative pain associated with spasm and inflammation. Drotaverine produces rapid pain relief due to antispasmodic action while Aceclofenac provides sustained analgesic effect. A fixed dose combination of Drotaverine with Aceclofenac is an effective and well tolerated therapy. Not only does it provides desired control of pain that is the primary aim of the treatment, but also controls inflammation and may contribute to healing process after abdominal operations. Combination of NSAIDs and antispasmodics has an established efficacy in most gynecological procedures and minor surgeries. The occurrence of postoperative pain and its intensity is influenced by the type of surgical procedures. In some of the laparoscopic surgeries which do not involve bowel resections or extensive bowel handling, early oral feeding can be initiated on return of bowel sounds owing to early postoperative recovery. Early administration of oral analgesics is possible in this group of surgeries. Therefore patients undergoing laparoscopic surgeries not necessitating prolonged bowel rest post-operatively were chosen for this study.

This study although the first of its kind demonstrates the benefits of Drotaverine and Aceclofenac combination in these selected group of patients. The efficacy and safety of this combination, has already been proved in dysmenorrhea. In this study although both the groups had shown good results with regard to pain scores however, the Group 1 showed significantly better resolution of postoperative pain because of comprehensive relief from pain associated with spasm and inflammation. Early resolution of pain would mean early ambulation, faster recovery and earlier return to normal activities.

Trauma and pain increase the levels of circulating catecholamines, which stimulate nausea and vomiting. It is a common finding that injured patients exhibit nausea as well as pain. Complete pain relief without relief of nausea is far less frequent (9.5%). Conversely, when pain relief is inadequate, nausea persists. In the present study adverse events like nausea, vomiting, dizziness etc. were considerably less in group 1 because of better pain relief than group 2. General

<table>
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<th>Table 2: Distribution of Patients into Group 1 and Group 2</th>
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<td>Group</td>
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<td>Total</td>
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<th>Table 3: Distribution of Patients according to age (p&lt;0.05)</th>
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<td>Group 1</td>
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<td>Age</td>
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<th>Fig. 2: Incidence of Adverse events</th>
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<th>Fig. 3: Global assessment score and general evaluation by doctor (p&lt;0.05)</th>
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evaluation by the doctor as per the questionnaire and Global Assessment Scores were also significantly higher (P<0.05) in Group 1 than Group 2. This study therefore shows that with minimal side effects the combination of oral Drotaverine and Aceclofenac can be recommended for oral analgesia following laparoscopic surgeries which do not involve extensive bowel handling.

CONCLUSION

Clinicians have always been on the lookout for better analgesia for expediting recovery in patients in the postoperative period. The present study showed that oral combination of drotaverine with aceclofenac is significantly more effective than aceclofenac alone in relieving postoperative pain following laparoscopic surgeries which do not involve bowel resections or extensive bowel handling like cholecystectomy, appendicectomy, nephrolithotomy or ureterolithotomy. The combination provides fairly early onset of pain relief and is well tolerated with minimal side effects.

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Causality Assessment of Adverse Drug Reactions in Tuberculosis Patients who are on Directly Observed Treatment Short Course Strategy in Mysore District

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ABSTRACT

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Tuberculosis (TB) is one of the foremost public health problems, curable disease if diagnosed and treated properly with antituberculosis drugs. In addition to disease related complications there are serious adverse drug reactions due to Anti-tuberculosis therapy. The present study was carried out to monitor, document and reporting of Adverse Drug Reactions (ADRs) in Tuberculosis patients who are on Directly Observed Treatment Short course (DOTS) strategy and to assess their causality by using Naranjo and WHO algorithms. This was a prospective observational and active surveillance study conducted over a period of 9 months. Each reported Adverse Drug Reaction was documented and assessed for its causality as per standard algorithms. A total of 128 Adverse Drug Reactions were identified out of which the prevalence of Adverse Drug Reactions in female was found to be 31.58% and 29.66% in male patients. The causality assessment by Naranjo's scale showed that out of 128 Adverse Drug Reactions, 128 (100%) Adverse Drug Reactions were probable and based on WHO probability assessment scale 119 (92.97%) were possible whereas as 9 (7.03%) were probable. The study concluded that Directly Observed Treatment Short course therapy is safer but regular monitoring of Adverse Drug Reactions should be adopted.

Keywords: Tuberculosis, Antituberculosis drugs, Directly Observed Treatment Short course, adverse drug reactions.

INTRODUCTION

Tuberculosis (TB) is a contagious infection caused by an airborne bacterium, Mycobacterium tuberculosis. Early days physicians referred Tuberculosis as Phthisis, derived from a Greek term for wasting, because its clinical presentation consisting of weight loss, cough, fever and hemoptyisis.

Based on the WHO surveillance and survey 9.27 million TB cases were found in 2007 (139 per 100000 population). Asia (South East Asia and Western Pacific regions) accounts for 55% of global cases, African region for 31% and other regions include America, Europe and Eastern Mediterranean accounts for a small fraction of global cases. India ranks first in the estimated number of Tuberculosis cases and approximately 1962 cases per 11, 69,016 population at the rate of 168 cases per 10,000,000 population. To control and reduce TB and its social burden Government of India in collaboration with WHO and World Bank launched a programme called RNTCP (Revised National Tuberculosis Control Programme).

A higher incidence of ADRs was noticed with antituberculosis drugs. Long duration of treatment for Tuberculosis with drugs like Isoniazid, Pyrazinamide, Rifampin, Ethambutol and Streptomycin causes adverse drug reactions like hepatotoxicity, visual disturbance, arthralgia, headache and skin rashes, mostly tend to occur in the first three months of therapy.

According to WHO, Adverse Drug Reaction (ADR) is defined as any 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 the modification of physiological function. Patients with multiple drug therapy are prone to develop an adverse drug reaction either due to alteration of drug effect through an interaction or by synergistic effect. Multiple or intercurrent disease, age, gender, race and genetics are also responsible for increased risk of developing an ADR.

Identification of an ADR can be useful for the prevention, early detection and management of ADRs. In ADR monitoring programs causality assessment of ADRs is an important step. Naranjo's algorithm and the WHO Probability scales are commonly used to carry out the assessment of causality of the ADRs. Hence, there is a need to study the safety of patients on DOTS through the monitoring of ADRs. According to WHO, pharmacovigilance is the science and activities relating to the detection, evaluation, understanding and prevention of adverse drug reactions or any other drug-related problems. Pharmacists have an ethical obligation to notify whenever ADRs are suspected and encouraged to report which in turn helps to minimize ADRs.

A large number of patients are exposed to anti-TB drugs at primary health centres (PHCs) in RNTCP/DOTS. In this context, this study was undertaken with the objectives to
monitor, document and reporting the ADRs in TB patients who are on DOTS strategy and to assess its causality by using Naranjo and WHO algorithms.

**MATERIAL AND METHODS**

**Study design:** This was a prospective observational and active surveillance study.

**Study site:** The study was conducted in the RNTCP/DOTS centers of Mysore district.

**Subjects:** All the patients from the study sites who were on DOTS for TB treatment/ newly started on DOTS were enrolled into the study after taking their consent.

**Study period:** Study duration was 9 months.

**Materials used:** TB treatment card, patient consent form, patient data collection form, suspected ADR notification form, Naranjo and WHO algorithms.

**Study procedure:**

The study protocol was approved from the Institutional Human Ethical Committee of Adichunchanagiri Institute of Medical Sciences (AIMS), BG Nagara before conducting the study. A written informed consent was taken from each patient before enrolling them in to the study. Patient information was collected from both the TB treatment card and also by interviewing the patient. The TB treatment card provides information regarding patient demographic details like age, weight, type of TB, HIV status, date of initiation of therapy, phase of treatment, date of completion of therapy and history of previous Anti-TB therapy. All the required information received from the patient was documented in the suitably designed patient data collection form. Information about the ADR experienced by the patient can be obtained by interviewing the patient. If ADRs were detected, they were brought to the notice of the medical officer for further evaluation. Details regarding the suspected drug, date of initiation of suspected drug, date of onset of reaction, brief description of the reaction were documented in the suspected ADR notification form and authenticated by the in charge medical officer. All the suspected ADRs were assessed for their causality by using the WHO ADR probability scale and Naranjo's algorithm. The documented data was subjected for suitable statistical analysis.

**RESULTS**

During the study period 175 patients were diagnosed with Tuberculosis who was on routine treatment protocol. Among 175 patients, 53 (30.28%) developed ADRs. Total number of adverse drug reactions detected in this was 128.

The prevalence of ADRs was more in the age group of 41-50 years (41.38%) followed by 33.33% at the age group of 61 years and above, and 30.77%, 28.57% at the age groups of 21-30, 11-20 years of age respectively. Female patients had higher prevalence of ADRs 31.58% when compared to males 29.66%. The prevalence of ADRs was higher in underweight patients 34.17% followed by overweight 33.33% and normal weight 21.15%. The former smokers were more prevalent to ADRs 32.9% than non-smoker 31.71% and current smoker 11.76%. The prevalence of ADRs was found high with non-alcoholics 32% followed by past or former alcoholics 30%. Current tobacco users were more prevalent to ADRs 100% than former tobacco users 32.26% and non-tobacco users 28.88%.

The prevalence of ADRs was found high with pulmonary TB 31.75% and followed with extra pulmonary TB 26.53%. The patients who were on intensive phase were more prevalent to ADRs 46.53% than who were on continuous phase 8.11%. The prevalence of ADRs was found high with Category II 42.11% followed by Category I 27%. The prevalence of ADRs was found more with patients having co morbids conditions 75% followed by the patients not having any co morbid conditions. Out of these 75% of patients, 85.71% had DM as shown in Table No. 01.

ADR's affected the Skin and appendages were high 27 (21.09%) followed by Gastro intestinal system 15 (11.73%), Musculo skeletal system 15 (11.72%), Central and peripheral nervous system 10 (7.81%), Vision 4 (3.12%). The most commonly identified adverse drug reactions affecting Skin were pruritis 27 (21.09%) followed by rashes 08 (06.25%), Gastro intestinal system were nausea 15 (11.73%), followed by vomiting 11 (08.59%), heart burn 02 (1.56%), diarrhoea, abdominal pain, flatulence 04 (03.12%), Musculo skeletal system were arthralgia and myalgia 15 (11.72%), Central and peripheral nervous system disorders were dizziness, headache 10 (7.81%) followed by neuropathy 08 (06.25%) and Vision was blurred vision 04 (03.12%) as shown in Table No. 02.

**Assessment scales:**

Causality assessment was done by using both Naranjo's and WHO scale. The assessment by naranjo's scale showed that out of 128 ADR's 128 (100%) were categorised as probable. The assessment done by using WHO scale revealed that out of 128 ADR's 119 (92.97%) were possible and 09 (7.03%) were probable as shown in Table No. 03. Out of 128 ADR's 128 (100%) were categorised as probable. The assessment done by using Naranjo's scale showed that out of 128 ADR's 119 (92.97%) were possible and 09 (7.03%) were probable. Out of 128 ADR's 119 (92.97%) were possible and 09 (7.03%) were probable. Out of 128 ADR's 119 (92.97%) were possible and 09 (7.03%) were probable. Out of 128 ADR's 119 (92.97%) were possible and 09 (7.03%) were probable. Out of 128 ADR's 119 (92.97%) were possible and 09 (7.03%) were probable. Out of 128 ADR's 119 (92.97%) were possible and 09 (7.03%) were probable.

**DISCUSSION**

In our study the prevalence of ADRs is comparatively more in the age group of 41-50 years. These observations are contrast to the study conducted by Gholami K et al. The prevalence of
ADRs observed in female patients (31.58%) was higher compared to male patients (29.66%), which was similar to the studies conducted by Gholami K et al. and Kishore PV et al. In underweight patients the prevalence of ADRs was observed more (34.17%) because of their low socio-economic status, poor nutrition and lack of awareness about the medication.

The prevalence of ADRs was more in non-alcoholics (32%) which were similar to the study conducted by Chhetri AK et al. But the prevalence of ADRs observed was more in former smokers (32.9%) and former tobacco users (32.26%) which were contrast with the study conducted by Chhetri AK et al.

Patients with the history of previous Anti-TB treatment, who were on intensive phase and Category II treatment, had the

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients (n=175)</th>
<th>No. of patients with ADR (n=53)</th>
<th>Prevalence</th>
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<tr>
<td>Age (in years)</td>
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<tr>
<td>01-10</td>
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<td>31-40</td>
<td>053 (30.30)</td>
<td>015 (28.30)</td>
<td>28.30</td>
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<td>029 (16.60)</td>
<td>012 (22.64)</td>
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<td>51-60</td>
<td>027 (15.40)</td>
<td>007 (13.21)</td>
<td>25.93</td>
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<tr>
<td>61 &amp; above</td>
<td>009 (05.10)</td>
<td>003 (05.67)</td>
<td>33.33</td>
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| Gender          |                         |                                 |            |
| Male            | 118 (67.40)              | 035 (66.04)                     | 29.66      |
| Female          | 057 (32.60)              | 018 (33.96)                     | 31.58      |

| BMI (kg/m2)     |                         |                                 |            |
| Underweight     | 120 (68.60)              | 041 (77.36)                     | 34.17      |
| Normal          | 052 (29.70)              | 011 (20.75)                     | 21.15      |
| Overweight      | 003 (01.70)              | 001 (01.89)                     | 33.33      |

| Smoking status  |                         |                                 |            |
| Former smoker   | 076 (43.40)              | 025 (47.17)                     | 32.90      |
| Current smoker  | 017 (09.70)              | 002 (03.77)                     | 11.76      |
| Non-smoker      | 082 (46.90)              | 026 (49.06)                     | 31.71      |

| Alcohol status  |                         |                                 |            |
| Former Alcoholic| 070 (40.00)              | 021 (39.62)                     | 30.00      |
| Current Alcoholic| 005 (02.90)             | 000 (00.00)                     | 00.00      |
| Non-Alcoholic   | 100 (57.10)              | 032 (60.38)                     | 32.00      |

| Tobacco use status |                         |                                 |            |
| Former Tobacco user| 031 (17.70)             | 010 (18.87)                     | 32.26      |
| Current Tobacco user| 002 (01.10)             | 002 (03.77)                     | 100.00     |
| Non-Tobacco user  | 142 (81.10)              | 041 (77.36)                     | 28.88      |

| Diagnosis       |                         |                                 |            |
| Pulmonary TB    | 126 (72.00)              | 040 (75.47)                     | 31.75      |
| Extra Pulmonary TB | 049 (28.00)           | 013 (24.53)                     | 26.53      |

| Phase of Anti-TB treatment |                         |                                 |            |
| Intensive Phase         | 101 (57.70)              | 047 (88.68)                     | 46.53      |
| Continuous phase        | 074 (42.30)              | 006 (11.32)                     | 08.11      |

| Category of treatment of TB |                         |                                 |            |
| Cat I                   | 137 (78.30)              | 037 (69.81)                     | 27.00      |
| Cat II                  | 038 (21.70)              | 016 (30.19)                     | 42.11      |

| Any other co morbid conditions and medications used |                         |                                 |            |
| Absent                  | 167 (95.40)              | 047 (88.68)                     | 28.14      |
| Present                 | 008 (04.60)              | 006 (11.32)                     | 75.00      |
| DM                      | 007 (04.00)              | 006 (11.32)                     | 85.71      |
| DM, HTN, AST            | 001 (00.50)              | 000 (00.00)                     | 00.00      |
higher prevalence of ADRs 40%, 46.53% and 42.11% respectively. The patients who had the history of previous Anti-TB treatment will be treated with Category II which includes Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin. The prevalence of ADRs increases with polypharmacy.6

The prevalence of ADRs was found to be higher in patients with only TB than in patients with co morbidities like Diabetes Mellitus, Hypertension and Asthma. Among these co morbid conditions, diabetes was found to be major. The lack of immune power in diabetic patients might be the reason for TB and prevalence of ADRs.

**Organ system classes involved in ADRs:**

Our study observed that skin and appendages was the most common organ system affected. It was noted that pruritus was found to be the major ADR 27 (21.09%). These findings were contrast to one of the study conducted at Imam tertiary care hospital, Iran.7

Gastrointestinal system was the second most organ system commonly affected. Observed ADRs included nausea which is major 15 (11.73%) followed by vomiting, heartburn, diarrhoea, abdominal pain and flatulence. Gastrointestinal system was found to be a common system affected due to ATT (Anti Tubercular Therapy) in the study conducted by Tak DK et al and Ghosh S et al.1,8

The occurrence of ADRs like arthralgia and myalgia were found to be 15 (11.72%). The study findings of arthralgia was related to that of the study conducted by Chhetri AK et al9,10 and Sharma TN et al.10

Dizziness was observed in 10 (7.81%) of the patients enrolled in the study. Similar results were found in the study conducted by Chhetri AK et al.10 Headache and neuropathy were also observed in our study which was related to the study conducted by Gholami K et al.10

Blurred vision was observed in 4 (3.12%) patients which is similar to the study conducted by Gholami K et al10 and Kishore PV et al11

**Assessment of ADRs:**

Naranjo algorithm is used widely for carrying out causality assessment of ADRs. It is based on the points given for each of ten questions that comprise the algorithm. After obtaining the points they were categorised under Definite ≥ 9, Probable 5-8, Possible 1-4, Unlikely ≤ 0. Majority of the patients showed probable under this scale, which is similar to the studies conducted by Gholami K et al10 and Kishore PV et al11

In the WHO assessment scale certain, possible, probable, unclassifiable, unlikely and unclassified were considered for assessing ADRs. 119 (92.97%) were possible and 09 (7.03%) were probable based on WHO scale which is similar to the study conducted by Tak DK et al.3

The main aim of DOTS strategy is to combat TB. Even though ADRs occur, there is no change in the treatment. In our study anti TB drugs were stopped only in one patient due to the severity of ADR and symptomatic treatment was given to few patients to subside the ADRs. Majority of the ADRs did not affect the therapy with the anti-TB drugs as they recovered without giving any symptomatic treatment.

**Limitation**

- Lack of laboratory investigations like plasma or tissue drug concentrations, liver function tests and haematological tests were not done.

**Future directions**

- Proper education should be given to the patients about the ADRs caused due to ATT which may reduce defaulter rates and would enhance medication adherence.
- Monitoring of ADRs induced by ATT in all RNTCP/DOTS centres should be explored.
- Implementation of spontaneous reporting system in the RNTCP/DOTS programme can be useful in identification of new ADRs to ATT.

**CONCLUSION**

This study showed that the prevalence of ADRs was high with first line anti-TB drugs (DOTS therapy). The adverse drug reactions increases remarkably as number of drugs rises. This study concluded that there is a need of a system for proper monitoring of ADRs caused by anti-TB drugs. Counselling of patients by a health care professional for timely prevention of ADRs is necessary as the treatment adherence can be achieved.

**ACKNOWLEDGEMENTS**

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**REFERENCES**


Comparison of Efficacy and Safety of Basal and Premixed Insulin Regimens among Type II Diabetes Patients Transiting From Oral Agents to Insulin

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INTRODUCTION

Type II diabetes mellitus is a progressive disease. Majority of the patients with type II diabetes are initially treated with dietary and lifestyle modifications and oral hypoglycemic agents (OHAs). Despite the therapeutic regimen, glycemic control deteriorates with time.1,2 In type II diabetes patients, micro- and macrovascular complications has been associated with poor glycemic control.3,4 Achieving glycemic control, preferably with hemoglobin HbA1c values of less than 7%, can markedly reduce the risk of such complications.4 The American Diabetes Association recommends that the objective of normalizing glycemia and glycosylated hemoglobin concentrations for patients with Type II diabetes should be similar to that for Type I diabetes.7

Achievement and maintenance of tight glycemic control require titration of the therapy by initiating insulin when oral hypoglycemic agents fail to achieve the HbA1C levels to the target. However, only a little proportion of patients having type II diabetes actually can achieve treatment goals and the number of patients requiring insulin therapy eventually rise.5,6 The results of a UK Prospective Diabetes Study (UKPDS) substudy and large observational PRESENT study revealed that initiation or early addition of insulin to oral therapy further improved the glycemic control in type II diabetic patients.11,12

The optimal insulin regimen in type II diabetes varies among physicians depending on the patient characteristics and guidelines released by diabetes federations. The most convenient and simple ways to initiate insulin treatment in patients with type II diabetes are most probably the use of long-acting basal insulin at bedtime or injection of premixed insulin before one or more meals.

While most studies support the notion that both basal and premixed insulin are better regimens, there is a lack of a uniform consensus as to which of the two regimens should be recommended to initiate insulin treatment in patients with type II diabetes.

The objective of this study is to compare the effectiveness of switching from oral hypoglycemic agents (OHA) to twice-

ABSTRACT

Introduction: Achievement and maintenance of tight glycemic control in type II diabetes require insulin when oral hypoglycemic agents fail to achieve target HbA1C. There is a lack of uniform consensus as to which of the regimens should be recommended to initiate insulin treatment in these patients.

Objectives: To compare the efficacy and safety of adding basal insulin to oral agents versus switching to twice-daily premixed insulin in type II diabetic patients insufficiently controlled by oral hypoglycemic agents (OHAs).

Research design and methods: This was a single-centre, retrospective study comparing glargine + OHA with premixed 70/30 regimen in patients with type II diabetes whose glycemic targets were not achieved with the use of oral hypoglycemic agents.

Results: A total of 138 subjects were eligible for this study. At study end, the mean HbA1c value was lower in the premix 70/30 than in glargine + OHA (8.07 ± 0.15 vs. 8.44 ± 0.17, P < 0.001). The HbA1c reduction was greater in the premix 70/30 than glargine + OHA (-2.316 ± 0.25 vs. -2.486 ± 0.24, respectively; P < 0.0001). More premix 70/30 treated subjects reached target HbA1c values than glargine treated subjects (HbA1c ≤ 7.0%: 31.4% vs. 26.5%). Similarly, FBG decrease was greater with premix 70/30 (mean difference -54.68 ± 17.93 vs -68.57 ± 9.17, P < 0.0001), and more patients reached target FBG < 110 mg/dl with premix 70/30 than with glargine + OHA (30% vs 25%). Premix 70/30 patients had fewer confirmed hypoglycemic episodes than glargine + OHA patients (14.3% and 20.6% respectively).

Conclusion: Based on the results, premixed biphasic 70/30 appears to be more effective than insulin glargine + OHA and a reasonable choice to initiate insulin therapy in insulin-naive subjects with type 2 diabetes that is not optimally controlled on OHA.

Keywords: Diabetes, OHA, retrospective, FBG, HbA1c
daily premixed human 70/30 insulin versus adding a once-daily injection of basal insulin glargine to the prior OHAs.

MATERIALS AND METHODS

This was a single-centre, retrospective study conducted at Asir Diabetes Center from June 2012 to June 2013 in accordance with Good Clinical Practice, comparing basal insulin regimen with premixed biphasic regimen in patients with type II diabetes whose glycemic targets were not achieved with the use of oral hypoglycemic agents. The study protocol was reviewed and approved by the Institutional Review Board.

Patients with Type II diabetes mellitus who were inadequately controlled while receiving oral hypoglycemic agents were recruited in the study after satisfying the following criteria: HbA1c >7%. Exclusion criteria for the study were patients with deranged liver function tests, serum creatinine >1.5 mg/dl, pregnancy, any other acute co-morbid illness, drug dependence and if he/she was unable to understand the regimen.

At the baseline visit, patients were randomized to either insulin glargine (Lantus; Aventis Pharma) given once daily in the morning in combination with the previous oral hypoglycemic agents (glargine plus OAD) or to human premixed insulin (30% regular, 70% NPH insulin; Humulin 30/70; Eli Lilly) to be administered twice daily (before breakfast and dinner), while other oral hypoglycemic agents were discontinued (70/30).

Data collected from the patient files included demographic characteristics, medical history, physical examination findings, diabetes related laboratory measurements and treatment recommendations in each visit. The patients were followed up in a scheduled manner every three months and the above data were recorded in each visit.

At the start of treatment, all patients were strictly educated about the application of insulin, use of insulin delivery devices (insulin pens), proper measurement and recording of blood glucose, awareness and management of hypoglycemia and nutrition. The patients were encouraged to self-measure their blood glucose levels every single day of the week at 7-point (before and 2 hours after each main meal and at bedtime) or 4-point (before each main meal and at bedtime) profile and were asked to report their measurements weekly the day after it was done to either diabetes nurse or doctor. At each visit, the patients were asked about compliance with insulin applications, meal planning, any hypoglycemia and its management, and all information gathered was recorded. The insulin dose titrations were done by the doctor.

Efficacy and safety measures:

The primary efficacy measure was the change in HbA1c level from baseline to end point. Secondary efficacy measurements were mean FBG level, proportion of patients with FBG levels ≤ 100 mg/dl and proportion of patients with HbA1c ≤ 7.0%. Safety measures were the proportion of patients with hypoglycemic events and the frequency of hypoglycemic events.

Statistical analysis:

The statistical analysis was carried out using graphpad prism version 5.01. All quantitative variables were estimated using measures of central location (mean, median) and measures of dispersion (standard deviation and standard error). Normality of data was checked by measures of skewness and Kolmogorov Smirnov tests of normality. For normally distributed data means were compared using student's t-test for two groups. For time related comparison paired t-test or Wilcoxon signed rank test was applied. Statistical significance considered at p <0.05.

Primary and secondary objectives:

The primary objective of this study was to compare the efficacy and safety of adding once-daily basal insulin versus switching to twice-daily premixed insulin in type 2 diabetic patients insufficiently controlled by oral hypoglycemic agents (OHAs).

The secondary objectives were to investigate the differences in fasting and postprandial blood glucose measurements, rate of improvement in HbA1c or blood glucose measurements, initial and mean insulin doses, incidence and rate of hypoglycemia.

RESULTS

A total of 138 patients were eligible for this study. There were 68 patients randomly assigned to OHA plus glargine (Group 1) and 70 patients were assigned to premix 70/30 (Group 2). Baseline demographic and clinical characteristics such as the age of the patients and the duration of diabetes were nearly similar between the treatment groups (Table 1). But the coexisting complications were more in group 1 patients, as shown in table 1.

Glycemic control:

Glycemic parameters are listed in Table 2. Patients in both groups had statistically significant improvement in the overall glycemic control during the study as evidenced by the decrease in HbA1c levels from 10.76 ± 0.18 per cent at randomization to 8.44 ± 0.17 per cent in group 1 and from 10.56 ± 0.19 per cent to 8.07 ± 0.15 per cent in group 2 after 12 months of treatment. The mean difference in HbA1c at the end of the study from the baseline in group 1 was -2.316 ± 0.25 per cent ([95% CI -1.8 to -2.8]) and was comparable with HbA1c reduction of -2.489 ± 0.24 per cent ([95% CI -2.03 to -3]) in group 2.
Of the total 138 patients, only 40 patients achieved HbA1c ≤ 7%, 18 patients (26.5%) from the group 1 and 22 patients (31.4%) from group 2 (p=0.37).

The mean fasting plasma glucose decreased from 209.8±6.1 to 155.1±16.9 mg/dl in group 1 patients and from 208.45±7.53 to 139.92±5.65 mg/dl in group 2 patients. Improvement in FBG was significantly better with premixed 70/30 compared with glargine plus OAD. A greater proportion of patients reached an FBG level ≤ 110 mg/dl with premixed 70/30 than with glargine plus OAD (30% vs 25%). The mean difference in FBG at the end of the study from the baseline in group 1 was -54.68 ± 17.93 mg/dl ([95% CI -54.8 to -86.9]) and -68.57 ± 9.178 mg/dl ([95% CI -50.6 to -86.6]) in group 2.

Weight gain:
Mean weight gain in patients treated with glargine plus OAD and 70/30 was 3.597 ± 2.4 and 4.531 ± 2.9kg, respectively. The mean BMI increased from 29.67±0.62 to 31.07±0.61 kg/m² in group 1 patients and from 31.07±0.86 to 32.82±0.82 kg/m² in group 2 patients.

Insulin dose:
There is a huge difference in the mean total doses of insulin between the two treatment groups at the start of the study; Insulin dose increased over the study duration from a mean daily starting dose of 13.91±1.11 to 32.03±1.86IU at endpoint for insulin glargine. The total dose (prebreakfast dose + predinner dose) increased from the mean starting dose of 50.89±2.66 to 62.54±3.22 IU at end point.

The mean difference in insulin dose at the end of the study from the baseline in group 1 was18.12 ± 2.176 IU ([95% CI 13.6 to -22.4]) and was 11.66 ± 4.180 IU ([95% CI 3.5 to 19.6]) in group 2. At the end of the study, the subjects required nearly twice as much daily insulin with 70/30 than with glargine plus OAD (62.54vs. 32.02IU). However, the insulin dose increment from the baseline was more in group 1 compared to group 2.

Change in HbA1c over 12 months:
The change in HbA1c over the 12 months in both the groups is shown in the table 3. Over the course of the study, HbA1c (Mean ± SE) declined in both groups (figure 1). The change in HbA1C is as follows: At the baseline, the HbA1c was 10.76 ± 0.18 and 10.56±0.19 for group 1 and group 2 respectively. At the first Visit [third month ] (group 1: 9.37±0.16%; group 2: 9.1±0.19%; p = 0.29), at the second visit [sixth month] (group 1: 8.61±0.18%; group 2: 8.33±0.16%; p = 0.27), at the third visit [ninth month] (group 1: 8.67±0.18%; group 2: 8.2±0.16%; p = 0.47) and at the fourth visit visit [twelth month] (group 1: 8.44±0.17%; group 2: 8.07±0.14%; p = 0.09). Decrement in Hb A1c was nearly same in both groups.
Despite use of these drugs, the therapeutic options for patients who fail initial therapy with combination of oral hypoglycemic drugs are either to add insulin or to discontinue the drugs and switch to insulin. Part of the rationale for combining an oral hypoglycemic drug with insulin therapy is that insulin can suppress hepatic glucose output, the primary cause of fasting hyperglycemia.

This study assessed two approaches for initiating insulin therapy in poorly controlled type 2 diabetic patients who have failed to achieve target glycemic control goals on OHA therapy. The results showed that, in poorly controlled type II diabetes patients who are on oral therapy, stopping OHAs and starting twice-daily premixed 70/30 insulin can provide more effective glycemic control than adding a single injection of insulin glargine to a combination of oral hypoglycemic agents. The reductions in HbA1c provided a clinical improvement for subjects in the premixed 70/30 group, allowing significantly more 70/30 treated subjects to achieve HbA1c targets established by the American Diabetes Association.

The results of this study were comparable to a similar study where insulin therapy was initiated with either twice-daily biphasic insulin lispro 75/25 or once-daily glargine, both taken concomitantly with metformin (17). Reduction in HbA1c was greater in the lispro premix group, and more subjects reached target HbA1c ≤ 7% in 16 weeks when treated with lispro premix than with glargine (41 vs. 22%, \( P \leq 0.001 \)).

In another study, therapy with once-daily glargine plus sulfonylureas and metformin was compared with twice-daily biphasic human insulin premix alone, without OHAs. In our study, the 70/30 insulin regimen enabled 31.4% of patients to reach HbA1c ≤ 7% without experiencing nocturnal hypoglycemia, whereas 26.5% of patients on glargine plus OHA achieved target HbA1c ≤ 7% in the absence of nocturnal hypoglycemia.

### Table 3: Change in HbA1c over 12 months

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Hba1c Level (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>2 OAD + Glargine</td>
<td>10.76±0.18</td>
</tr>
<tr>
<td>Premixed insulin 30/70 +metformin</td>
<td>10.56±0.19</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.45</td>
</tr>
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</table>

### Table 4: Number of patients affected by hypoglycemic events.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Regimen</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>Glargine + OAD</td>
<td>10</td>
<td>14.7</td>
</tr>
<tr>
<td></td>
<td>70/30</td>
<td>14</td>
<td>20</td>
</tr>
</tbody>
</table>

### Hypoglycemia:

14 patients (20.6%) receiving glargine plus OAD and 10 patients (14.3%) receiving premixed 70/30 experienced at least one hypoglycemic event (table 4). None of the patients required hospital admission for these episodes. Hypoglycemia was mostly recorded to be related to incompatibility with life style. None of the patients had severe hypoglycemia. Hypoglycemia affected elderly patients slightly more (57.1%) than the young patients (42.9%) in group 1, whereas Hypoglycemia affected young patients more (60%) than the elderly patients (40%) in group 2.

### DISCUSSION

The prevalence of type II diabetes mellitus is a common nowadays, and is responsible for excess morbidity and mortality, micro and macro vascular complications, and impaired quality of life. Recent UKPDS study and other studies have highlighted the significance of achieving tight glycemic control to prevent such complications.

Initial treatment should begin with diet, weight reduction and exercise, which can induce normoglycemia if compliance is optimal. Patients with persistent hyperglycemia are typically started on one or more oral hypoglycemic agents. Insulin has traditionally been used only if inadequate control persists despite use of these drugs. The therapeutic options for patients who fail initial therapy with combination of oral hypoglycemic drugs are either to add insulin or to discontinue the drugs and switch to insulin. Part of the rationale for combining an oral hypoglycemic drug with insulin therapy is that insulin can suppress hepatic glucose output, the primary cause of fasting hyperglycemia.

This study assessed two approaches for initiating insulin therapy in poorly controlled type 2 diabetic patients who have failed to achieve target glycemic control goals on OHA therapy. The results showed that, in poorly controlled type II diabetes patients who are on oral therapy, stopping OHAs and starting twice-daily premixed 70/30 insulin can provide more effective glycemic control than adding a single injection of insulin glargine to a combination of oral hypoglycemic agents. The reductions in HbA1c provided a clinical improvement for subjects in the premixed 70/30 group, allowing significantly more 70/30 treated subjects to achieve HbA1c targets established by the American Diabetes Association.

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![Fig. 1: Change in HbA1c over 12 months.](image-url)
The events of hypoglycemia increase obviously when patients use insulin to achieve better glycemic control and defined glycemic targets. It is obvious that the overall incidence of minor hypoglycemia would be greater in the 70/30 group than in the glargine group considering that the 70/30 group had better glycemic control than the glargine group. Importantly, hypoglycemia was not a barrier to achieving glycemic targets for the 70/30 group. Studies show that increased risk of hypoglycemia is associated with intensive glycemic control using insulin, all the patients who are initiated with insulin therapy should always be referred to diabetes self management training programs to help them prevent, recognize, and manage their hypoglycemic episodes.

Initiation of insulin therapy is often accompanied by an increase in weight as glycemic control improves. The weight gain was more in 70/30 group in comparison with the glargine group, which is consistent with similar previous studies in both the treatment groups. The reason for the reduced weight gain with the glargine group may be the addition of metformin as a concomitant therapy, as reported by the previous studies.

Since patients randomized to the 70/30 group did not receive any OHAs, this study compared two regimens for initiating insulin rather than two specific forms of insulin. However, previous studies using NPH insulin in combination with OHAs showed lower weight gain in comparison to insulin monotherapy with premixed insulin.

In clinical practice, OHAs are often discontinued once a 70/30 insulin regimen is begun, but continuing metformin might be expected to improve the effectiveness of this regimen. Clearly, many questions remain regarding the initiation of insulin therapy in patients with type 2 diabetes. The current study provides efficacy and safety data pertaining to two commonly used insulin regimens. Further studies are required to provide physicians with additional guidance. These should include addressing the benefit of 70/30 insulin plus metformin combination to ascertain the level of influence of metformin on the results obtained in the insulin glargine–treated group.

In addition, it would be of interest to compare the glargine plus OHA regimen with a rapid acting analog plus NPH insulin as use of the latter insulin regimen becomes more widespread. The relative costs of treatment with all of these regimens, including the glucose testing required by each, should also be studied. Finally, despite the improvement in control achieved by 70/30 insulin regimen, over Three quarters of patients in the 70/30 group did not reach HbA1c \( \leq 7\% \).

Insulin therapy is typically begun only after lifestyle modification and OHA therapy fail to normalize HbA1c values. In general, most individuals with type II diabetes rarely are started on insulin with HbA1c values \( \geq 8.5\% \). Unfortunately, many subjects will have had type II diabetes for 10–15 years before diagnosis and may have already developed complications. Therefore, earlier introduction of the most effective insulin therapy should be encouraged despite the reluctance of patients and their physicians.

Based on the results of this study, premixed 70/30 regimen appears to be more effective than insulin glargine + OHA and a reasonable choice to initiate insulin therapy in insulin-naive subjects with type II diabetes that is not optimally controlled on OHA therapy.

REFERENCES


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Implementation of Self Reporting Pharmacovigilence in Anti Tubercular Therapy using Knowledge Based Approach

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ABSTRACT

Tuberculosis (TB) hampered with poor patient compliance and intolerance at least partially due to adverse drug reactions (ADRs). A prospective observational and interventional healthcare teamwork study was carried out to implement a self reporting pharmacovigilence system in TB patients through a knowledge based approach in the pulmonology department of Kovai medical center and Hospital (KMCH) at Coimbatore. A patient information pamphlet which was endorsed by the pulmonology associates was the core tool for this study. A well practiced and skilled clinical pharmacist educated the patients and enabled them to report the ADRs due to anti tubercular drugs through the emergency number given in the pamphlet. Totally 110 patients enrolled in the study. 43 (39%) patients experienced 74 numbers of ADRs during the intensive phase therapy. Out of 110 patients, 101 were adhered to the intensive phase therapy. Of the 74 ADRs experienced tot he study population, 24 ADRs were occurred in 18 patients which are needed to be self reported by the patient according to the study protocol. Among 24 ADRs which have to be self reported, 20 (83.33%) ADRs were reported through 17 calls by 16 patients. The self reporting pharmacovigilence for anti tubercular therapy in pulmonology department of KMCH, Coimbatore, were implemented and was certified by the pulmonology associates. Our Study concludes that if a proper educational system is implemented, most of the patients were ready to report their ADR of any drug and thereby we can improve both patient adherence and reducing the severity of ADRs. It is suggested that the pharmacists should exhibit their vital role during TB therapy in TB centers, pulmonology departments and DOTS centers to guarantee a better patient care.

Keywords: Self reporting pharmacovigilence, Anti-TB drugs, Clinical pharmacist, ADR reporting system

INTRODUCTION

Tuberculosis (TB) is the most rampant communicable infectious disease on earth and remains out of control in many developing nations. Good patient adherence to the treatment regimens is the foundation stone to effective Anti Tubercular Therapy (ATT). Alas, non compliance is cited as the major problem to the control of tuberculosis at the level of public health and finally which escort to the drug resistance in case of TB. ATT exhibits greater level of efficacy with a satisfactory degree of toxicity; however combination treatment may produce severe adverse events. Important adverse effects are hepatitis, join pain, skin rash, gastro intestinal upset (nauses/vomiting/GI upset), hyperuricemia, Constipation, peripheral neuropathy, and visual disturbances. TB hampered with poor patient compliance and intolerance at least partially due to the ADRs. According to World Health Organization (WHO) and several other studies concluded that, the poor out-come was attributed to poor patient compliance, to primary multidrug resistance and to interruption partially due to ADR (WHO 1997) and the towering incidence of TB infection has caused a high occurrence of morbidity and mortality which is partly due to serious ADRs induced by Anti- TB drugs.

Patient's decisions to stop taking medications were influenced by a number of interacting factors. The lack of knowledge about the treatment and ATT induced ADRs are the two major factors which leads to the patient's non-adherence to the TB therapy. A qualitative and quantitative study by Weiguo X et al. stated that almost 16 factors which leads to the non-adherence for the TB treatment. Majority of them are due to the lack of knowledge about the importance of the completion of therapy. Out of these 16 factors 37.80% (which is the highest percentage) of patients were non adherent due to the severe ADRs. Schaberg T et al. were also stated that 26% of

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TB patients in the study population were discontinued therapy due side effects.\(^7\)

The influence of side effects – real, anticipated or interpreted on compliance to treatment was mentioned in a number of studies. Some patients reported stopping medication due to adverse effects while others complained that they were not educated about side effects and what to do to counter them.\(^5\) In-depth interviews among both TB patients and local doctors point out that ADR is a motive for treatment non-adherence. Worry of the risks of ADRs leads some TB patients to break off the treatment.\(^26\) “... I don’t want to take these pills, because they make me sick, they hurt me...” (Female TB patient, Bolivia) is an example for the same.\(^7\) Local health workers often cannot find out this discontinuation of treatment due to the lack of an ADR surveillance system under the current DOTS program.\(^20\) Counseling of patients for timely hindrance, revealing and management of ADRs was also highly suggestive.\(^11\) Also it is already proved that patients were clearly willing to report symptoms which they believe to be due to a particular prescribed drug if they were informed about it. So it is fundamentally required a system for proper monitoring of ADRs due to anti tubercular drugs. Several studies were suggesting the significance of a new system for premature detection of ADR for a better patient care.\(^5,11,21\)

This leads to the taking a decision to do an intervention of a new health care teamwork approach with an intention to complete patient care during ATT with a special preference on ADR reporting system. The evidence of patient’s definite role in ADR and their willingness to report the ADR\(^21,22,25,26\) were planned to utilize in this study by expecting a good adherence. Here comes the importance of pharmaceutical care based approach to the TB patient. This study is one of the clinical pharmacy come health care team work oriented one, aiming for the best quality of life of tuberculosis patient during their therapy by implementing an educational approach to them regarding on both the therapy and how to counteract the possible ADRs during Anti Tubercular Therapy.

**MATERIALS AND METHODS**

The present study is Prospective observational and interventional study conducted in Department of pulmonology, of an 800 bedded super specialty hospital at Coimbatore, Tamilnadu, for a period of 8 months. Study was approved by the concerned authorities. Both the inpatients and outpatients who received the prescription of Anti Tubercular drugs aged between 16 to 75 years were included in the study Even though we are given the education, patients who referred to their nearest clinic or physician for continuation the treatment after diagnosing from the present study site, were excluded from the study. Also patient who has MDR TB, patients with co-morbidity medical/surgical condition and mentally retarded patients were excluded.

A patient information pamphlet named as “Things to be noticed while taking medicines for tuberculosis” (both in tamil and english) which was evaluated and validated by the pulmonology physicians is the core tool for this study. This is particularly prepared for enabling and initiating the patient to report the ADR. The pamphlet provide the information’s on TB, possible ADR during ATT and the emergency contact number of both the physician and pharmacist to report ADR by the patient itself once if they suspect the ADR. Adverse drug reactions which are illustrated in the patient information pamphlet were only considered to evaluate effectiveness of self reporting pharmacovigilence system. They include nausea/vomiting, joint pains, loss of appetite, weight loss, yellow colorations of eye and skin, vision problem, skin itch/rash and abdominal pain. ADR incidence during the time of hospital period was excluded from the self report. Calls received which are not related to ADR were also excluded from report.

**Educational module**

A well experienced and skilled pharmacist thoroughly educated the tuberculosis patient regarding the disease, duration of the treatment, importance of treatment completion and about possible adverse effects by using the pamphlet. Ultimately the pharmacist enables the patient to screen the ADR given in the pamphlet during the treatment and how to tackle them. The knowledge was evaluated after the counseling for analyzing the knowledge of the patient regarding his treatment. And re-counseling was performed if it is necessary.

**RESULTS AND DISCUSSION**

The study was carried out in the pulmonology department of Kovai Medical Center and Hospital at Coimbatore, over a period of 8 months from May to December 2010. Study results were summarized in table 1 and 2. A total of 110 patients were incorporated in the study. Of the whole population 63 (57.27%) were inpatients and 47 (42.73%) were outpatients. Among the total population, 77 (70%) were male and 33 (30%) were females. It is found that males were more prone to tuberculosis when compared to females with a ratio of 7:3. A study conducted by Mahmood I et al., reveals that the pervasiveness of tuberculosis is more in males than females with a ratio of 5:1. Also the National Tuberculosis Program (NTP) summarized as the ratio of the occurrence of TB between the male and female were 5:2.\(^7\) One of the study performed by Jaggarajamma K et al., has the identical outcome alike to ours in case of the gender wise occurrence of the TB, which contributes that a 7:2.5 ratio of male and female incidence of TB.\(^19\) Not only these studies, some other studies also point out that the TB is more prone to male gender like in our study.\(^19,30,10\)
The mean age of the study population was found to be 45.61±15.26. Previous data’s regarding the age group who were more prone to TB shows dissimilar conclusions. According to RNTCP status report (TB India 2006) TB affects habitually in young adults with an age range of 25-34. A review through some other studies also reveals the same. A descriptive study executed by Habib-ullah K et al., reveals that the mean age group for TB occurrence is 42.10±20.38. The mean age of the TB patients from the study population of Marra F et al., were also found to be 49.9±20.9. Both of these two studies were supporting to the current study outcome.

Among the total population 93 (84.55%) were married. Literacy status of entire population justified that 54 (49.09%) patients have a literacy level of “1-10”. Out of the study population 78 (70.91%) patients were not having the smoking habit.

In our study about 85 (77.27%) patients were diagnosed as pulmonary TB in our study population. About 92% of the populations in the research of Jaggarajamma K et al. were diagnosed as Pulmonary Tuberculosis (PTB). A study reported by Habib-ullah K et al., interpret that 73% of the study population were diagnosed as PTB which was matching to our study. Of the remaining patients in our study, 7 (06.36%) patients were diagnosed to have miliary TB and the remaining 1 (00.91%) patient was diagnosed as spinal TB. It shows that when compared to EPTB, PTB shows most occurrences as per the prior study conclusions.

Among the full population 43 (39.09%) patients experienced at least one ADR during the time of study period. The prevalence of ADR occurrence as per three different studies during the intensive phase of ATT were found to be 22%, 30%, and 55%.

Out of 43 ADR victims 29 (67.44%) were male and 14 (32.59%) were females. Majority of them were males and the statistically there is no significant relation between the

### Table 1: Demographic data and occurrence of TB in all patients

<table>
<thead>
<tr>
<th>Parameters of all Patients</th>
<th>Frequency (%) (N=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of patient</td>
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</tr>
<tr>
<td>Inpatients</td>
<td>63 (57.27%)</td>
</tr>
<tr>
<td>Outpatients</td>
<td>47 (42.73%)</td>
</tr>
<tr>
<td>Gender</td>
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</tr>
<tr>
<td>Males</td>
<td>77 (70%)</td>
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<tr>
<td>Females</td>
<td>33 (30%)</td>
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<tr>
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<td>46-60</td>
<td>43 (39.09%)</td>
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<tr>
<td>61-75</td>
<td>16 (14.54%)</td>
</tr>
<tr>
<td>Literacy Level</td>
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</tr>
<tr>
<td>Illiterate</td>
<td>29 (26.36%)</td>
</tr>
<tr>
<td>01-10th class</td>
<td>54 (49.09%)</td>
</tr>
<tr>
<td>Above 10th</td>
<td>27 (24.55%)</td>
</tr>
<tr>
<td>Smoking Habits</td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>32 (29.09%)</td>
</tr>
<tr>
<td>Non smokers</td>
<td>78 (70.91%)</td>
</tr>
<tr>
<td>Types of TB</td>
<td></td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>85 (77.27%)</td>
</tr>
<tr>
<td>TB lymphadenitis</td>
<td>07 (06.36%)</td>
</tr>
<tr>
<td>TB pleuritis</td>
<td>07 (06.36%)</td>
</tr>
<tr>
<td>TB pleural effusion</td>
<td>04 (03.64%)</td>
</tr>
<tr>
<td>Silico TB</td>
<td>04 (03.64%)</td>
</tr>
<tr>
<td>Miliary TB</td>
<td>02 (01.81%)</td>
</tr>
<tr>
<td>Spinal TB</td>
<td>01 (00.91%)</td>
</tr>
<tr>
<td>ADR</td>
<td></td>
</tr>
<tr>
<td>ADR developers</td>
<td>43 (39.09%)</td>
</tr>
<tr>
<td>ADR non developers</td>
<td>67 (60.91%)</td>
</tr>
</tbody>
</table>

### Table 2: ADR occurrence

<table>
<thead>
<tr>
<th>Parameters of ADR Experienced Patients</th>
<th>Frequency of ADR (%) (N=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (67.44)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (32.59)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
</tr>
<tr>
<td>16-30</td>
<td>08 (18.60)</td>
</tr>
<tr>
<td>31-45</td>
<td>10 (23.26)</td>
</tr>
<tr>
<td>46-60</td>
<td>20 (46.51)</td>
</tr>
<tr>
<td>61-75</td>
<td>05 (11.63)</td>
</tr>
<tr>
<td>ADR Reported</td>
<td></td>
</tr>
<tr>
<td>Elevated liver enzymes/hepatitis</td>
<td>17 (22.97)</td>
</tr>
<tr>
<td>Nausea &amp; vomiting</td>
<td>13 (17.57)</td>
</tr>
<tr>
<td>Joint pain</td>
<td>07 (09.46)</td>
</tr>
<tr>
<td>Skin rash/itch</td>
<td>06 (08.11)</td>
</tr>
<tr>
<td>Headache</td>
<td>05 (06.76)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>04 (05.41)</td>
</tr>
<tr>
<td>Dysurea</td>
<td>04 (05.41)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>03 (04.05)</td>
</tr>
<tr>
<td>Back/body pain</td>
<td>03 (04.05)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>03 (04.05)</td>
</tr>
<tr>
<td>Tiredness</td>
<td>03 (04.05)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>02 (02.70)</td>
</tr>
<tr>
<td>Loss of weight</td>
<td>01 (01.35)</td>
</tr>
<tr>
<td>Giddiness</td>
<td>01 (01.35)</td>
</tr>
<tr>
<td>Visual problem</td>
<td>01 (01.35)</td>
</tr>
<tr>
<td>Pedal edema</td>
<td>01 (01.35)</td>
</tr>
</tbody>
</table>
occurrence of ADR and gender.\textsuperscript{11,12} The most prone age group for ADR incidence was found to be ‘46-60’ group comprising of 20 (46.51%) patients followed by ‘31-45’ group which includes about 10 (23.26%) patients. This result is controversial to the study of Anupa KC et al., in which the most prominent age group for the occurrence of ADR for ATT were belongs to ‘21-30’ group. The statistical result shows that there is no significant relationship between the age and ADR which is similar to the previous study.\textsuperscript{11} While evaluating the age group for major ADR in gender wise, 18 (62.07%) male patients were belongs to the age group ‘46-60’, and 5 (35.71%) female patients were in the age group of ‘31-45’.

A total of 74 ADRs have been experienced by these 43 patients, the pattern of ADR have been represented in the table 2. Among the 43 ADR victims 23 (53.49%), 12 (26.91%), 5 (11.62%) and 3 (06.98%) patients showed one, two, three and four different ADR’s respectively (Fig: 1). Out of 74 ADRs, 17 (22.97%) were elevated liver enzymes, which is the most prominent one followed by vomiting and joint pain. Drug induced liver problem is not a rare problem in ATT. It is seen that a 20% hepatotoxic ADR victims in the study of Khalid M et al.,\textsuperscript{8} Previous studies proved that liver and biliary system and gastro intestinal system were the most frequent organ system for the development of ADRs for anti tubercular drugs.\textsuperscript{10,12} It shows that hepatitis followed by the vomiting were the major ADRs occurred in the population of the study of Marra F et al., which is similar to our study.\textsuperscript{10} The time interval between start of therapy and onset of ADR is demonstrated in Fig 2. It was found that 37 (50%) ADRs occurred within 15 days after starting the therapy. An overview of the Fig 2 shows that as there is a decreased incidence of ADRs when the days get increased. This is quite similar to the study of Kheirollah G et al.,\textsuperscript{12}

The categorization of the observed ADRs on the basis of exclusion and inclusion criteria of our study protocol was summarized in table 3. Out of 74 ADRs, 16 during the hospital stay only. Remaining 58 ADRs were occurred during the whole review period, in which 34 were excluded from the self report. 24 ADRs were included in the category, which is need to report according to the study protocol.

Of the total population 81 (73.64%) patients came for the first review without ADR, and 25 (22.73%) patients came for review with 32 numbers of ADR and 4 (03.64%) patients did not turn up for the review. Vomiting followed by skin rash and anorexia occurred mostly during the first review period which belongs to the inclusion criteria of the study evaluating protocol. Coming to the second review, 88 (80%) patients came for the review without ADR while, 16 (14.55%) patients came for review with 23 numbers of ADR. It was observed that the number of non compliant patient increased from 04 to 06 (05.45%) from first review. Joint pain followed by skin rash occurred most of the times during the second review which belongs to the inclusion criteria of the study evaluating protocol. In third review, Of the total population 99 (90%) were came for review without ADR whereas 2 (01.82%) patients came with 3 numbers of ADR. After reaching to the

<table>
<thead>
<tr>
<th>Table 3: ADR occurrence in each review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>1st review</td>
</tr>
<tr>
<td>2nd review</td>
</tr>
<tr>
<td>3rd review</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Fig. 1. Distribution of patients on the basis of number of ADR(s) occurred (N=43)

Fig. 2: Duration of ADR(s) occurrence after starting therapy (N=74)
last review of our study the non complaints level is again increased from 06 to 09. Only joint pain occurred during the third review period which belongs to the inclusion criteria of the study evaluating protocol.

At the end of two months follow up of the study population, 9 (08.18%) patients dropped out from the study. Communicating through telephones reveals that 4 of them continuing therapy in other hospital. 3 of them don’t have the response. 2 were non-adhered. It was observed that 101 (91.82%) patients were adhered to the treatment till the completion of the intensive phase. It is a great level of the compliance, and this adherence level is the directly related to the interventional educational program and the good communicative patient care system in our study. The incidence of ADR is descending order to the review period.

A total of 17 calls were received from 16 patients (1 patient called 2 times) by reporting 20 numbers of ADR [Tab 3]. Out of 24 ADRs need to report, 20 (83.33%) ADRs were reported by 16 (88.88%) patients and 4 (16.67%) ADRs were not reported by 2 (11.11%) patients [Fig 3 and 4]. The result shows that a high percentage of patients were ready to report ADRs if the healthcare professionals give the knowledge regarding the same. A study conducted by Jarernsiripornkul N et al., concluded that patients were ready to report the symptoms which they believe to be due to a specific prescribed drug and it will help the early detection of ADR and thereby we can reduce severity of the same.\textsuperscript{22,23}

About 39% of patients suffered diverse types of ADRs due to ATT in the pulmonology department of our hospital during the period of study. Predominantly it is a privileged percentage of ADRs, to take a decision for implementing a good patient care oriented program by the health care professionals. As a pharmacist, we have the liability to support the patients during the periods of ATT, while they were suffering these kinds of unwanted effects of the drug. These unwanted effects may steer the patient to make a judgment for stopping the medications and finally the occurrence of drug resistance and an amplified healthcare cost.

CONCLUSION

The attempt of implementation of self reporting pharmacovigilence for ATT in pulmonology department of Kovai Medical Center and Hospital was done, and which was authorized by the pulmonology associates. The study realized that If a proper educational system is implemented like our study, most of the patients were ready to report their ADR and thereby we can improve both the patient adherence and therapeutic outcome. Also a good constitutional system of communicational approach to the patient by group effort of the pharmacist and physician with the aim of complete patient care will aid for early detection of the ADRs of any drug and can trim down the incidence and severity of the same. Since DR (Drug resistance) is the major emerging problem during ATT, implementation of well communicated system like self reporting pharmacovigilence will help to hoist the patient's self-assurance in the treatment and reduced incidence of DR. It is suggested that the community pharmacists and clinical pharmacists should exhibit their vital role during TB therapy in TB centers, pulmonology departments and DOTS centers to guarantee a better patient therapeutic outcome.

ACKNOWLEDGEMENT

The authors acknowledge Dr. Nalla G. Palanisamy Chairman, Managing Director, Kovai Medical Center and Hospital, Coimbatore and Dr. Thavamani D. Palanisamy Trustee Kovai Medical Center Research and Educational Trust, Coimbatore for providing necessary facilities and constant encouragement. We widen our heartfelt and truthful thankfulness to Dr. V. R. Pattabhiraman, M.D, DIPNB., Consultant Respiratory Sleep Medicine, and Dr. S. Mahadevan, M.D., Consultant Respiratory medicine, for their expensive guiding principle in the exposition work. We are really courtesies and pleased to them for openedhanded an opportunity to work along with them. I put across my honest thanks and gratitude to our Principal, Prof. Dr. A. Rajasekaran, M.Pharm., Ph.D., KMCH College of Pharmacy, for providing me with a cooperative and artistic milieu to facilitate us to work outstandingly. We coverage our thanks to
the patients and their family members involved in my study, who gave their chock-full mutual aid in all the stages of this thesis study.

REFERENCE


The prevalence and the number of people living with diabetes in India is increasing every year, which imparts a burden on the economic growth. The studies related to the healthcare cost of diabetes are limited in India. A prospective observational study was carried out for a period of seven months with the aim to determine average annual per patient direct cost for management of type 2 diabetes mellitus, to determine the average annual per patient direct cost for diabetic patients having micro and macro vascular complications, and the factors affecting the healthcare cost. The average annual per patient direct cost for management of type 2 diabetes is 38,589 rupees. Diabetes patients who did not have any complications spent 15,512 rupees as average annual per patient direct cost for their care. Patients with one complication spent 25,228 rupees as average annual per patient direct cost for their care. Patients with three complications spend 52,607 rupees as average annual per patient direct cost for their care. The factors affecting healthcare cost and hospitalization were the medicine cost, lab investigation cost, hospital admission cost, presence and severity of diabetes associated complications. Cost of illness studies can provide a framework for estimation of cost estimation for Cost Effectiveness and Cost Benefit Analysis, the methods which are commonly employed for decision making while updating the formulary. Pharmacist can perform his role when making formulary decisions as a member of Pharmacy and Therapeutic Committee (PTC), using the information gathered from pharmacoeconomic evaluation.

**Keywords**: Diabetes Mellitus, Pharmacoeconomics, Healthcare Cost, Cost of Illness, Direct Cost, Annual Medicine Cost, Annual Lab Cost, Annual Consultation Cost.

**INTRODUCTION**

According to IDF atlas 5th edition update India is having a total diabetes population of 61.3 million, which is just behind China having a total diabetes population of 92.3 million. The prevalence of type 2 diabetes mellitus is rising in alaromic scale in India, which poses a major threat to clinical management, economic growth and social wellbeing of patients. Financial burden is more on the individuals who have diabetes and associated co-morbid condition than those who have only diabetes.

**DIABETES MELLITUS**

Diabetes (DM) is a group of metabolic disorders characterized by hyperglycaemia: associated with abnormalities in carbohydrates, fat and protein metabolism; and resulting in chronic complications including microvascular, macrovascular and neuropathic.

**CLASSIFICATION**

1) Type 1

Type 1 diabetes mellitus is characterized by destruction of pancreatic beta cells.

2) Type 2

May range from predominantly insulin resistant to predominantly insulin deficient.

3) Gestational diabetes mellitus

Defined as any degree of glucose intolerance that has its onset or is first detected during pregnancy. Occurs in 2-4 % of pregnant woman, generally during the second or third trimester.

4) Other specific types (secondary diabetes) - Broad term used to classify patients who have unusual causes of diabetes owing to certain diseases of the pancreas, genetic defects, endocrinopathies, or drugs.

**Type 1A Immune-Mediated Diabetes**

This type is characterized by an absolute deficiency of insulin.

**Idiopathic Type 1B Diabetes**

Idiopathic type 1B diabetes is used to describe those cases of beta cell destruction in which no evidence of autoimmunity is present.

**Type 2 Diabetes Mellitus**

Type 2 diabetes mellitus is a heterogeneous condition that
describes the presence of hyperglycemia in association with relative insulin deficiency.

LONG-TERM COMPLICATIONS

A. Macrovascular complications (coronary artery, cerebrovascular and peripheral vascular disease)
1. Atherosclerosis (coronary, cerebrovascular and peripheral vessels) occurs at an earlier age than nondiabetic individuals.
2. Peripheral vascular disease may lead to pain, chronic cold feet, or insufficient circulation to enable healing of distal lesions (ultimately leading to gangrene and amputation).
3. Hypertension (HTN) Co-existence of HTN and DM strikingly increases the risk of cardiovascular disease, doubles the risk of cardiovascular death, and increases incidence of stroke and transient ischemic events in DM individuals.

B. Eye Diseases
1. Diabetic retinopathy
   a. A consequence of microvascular changes. Most prevalent eye complication and is often detectable within 5 years after the diagnosis of DM.
   b. There are mainly three types of retinopathy
      • Non proliferative retinopathy
      • Preproliferative retinopathy
      • Proliferative retinopathy

C. Diabetic nephropathy: Renal failure occurs in 30-40% of patients with type1 DM within 30 years after diagnosis and 20-30% of patients with type 2 DM.

D. Diabetic neuropathies
1. Peripheral neuropathy: The sensorimotor nervous system is most often affected, but sympathetic or parasympathetic abnormalities may be present also.
2. Autonomic neuropathy: It involves multiple systems throughout the body.

E. Foot, skin, and mucous membrane complications: These problems stem from vascular change and peripheral neuropathy that cause alterations in the nerves that control blood flow and skin hydration.5,6

NEED FOR PHARMACOECONOMICS
Pharmacoeconomics offers assistance under resource constraints, tight budgets and competing programmes. It can aid in decision making in evaluating the affordability of and access to the right medication to the right patient at the right time, comparing two drugs in the same therapeutic class or drugs with similar mechanism of action and in establishing accountability that the claims by a manufacturer regarding a drug are justified.7

Cost of Illness Analysis (CIA):
It may be defined as the evaluation and assessment of the resources used in treating an illness.8

Types of costs and perspectives used in analysis

Direct Cost
Direct economic costs of disease are those generated by the resources used in treating or coping with a disease, including expenditures for medical care and the treatment of the illness (hospital care, physician services, nursing home care, drugs and other medical needs).

Indirect Cost
Indirect costs consider the potential resources that are lost as a result of a disease. They include the societal costs of morbidity, disability and premature mortality. eg: lost productivity, care giver costs, and quality of life.

Intangible Cost
Non-financial outcomes of disease and medical care.

Perspectives
A cost-of-illness study may be conducted from several different perspectives, each of which includes slightly different costs.

Uses of Cost of Illness study
The data from Cost-of-Illness studies are used in determining budgetary allocations, prioritizing research funding and justifying funding for disease projects. Knowledge of the costs of an illness can help policy makers to decide which diseases need to be addressed first by health care and prevention policy.9

NEED OF THE STUDY
There are very few studies quoting direct cost of diabetes care.10 Major studies which estimated the cost of care for diabetes are the following. A study by Rayappa et al estimated that the annual direct cost of routine care in 1998 was about US$191 (about 8595 rupees) and the mean direct cost and hospitalization for a diabetes related episode was about US$208 (9360 rupees). A study by Kapur et al in year 2000 found that the annual direct cost of ambulatory care for
diabetes was 4724 Rupees. Shobhana et al. conducted a study to estimate the health care expenditure for type 1 and type 2 diabetes in the year 2000 and the study found that the expenditures as 8578 and 3310 rupees respectively. Study conducted by Viswanathan V et al. in 2009 found out that the total direct per annum for the management of diabetes was 25391 rupees. Diabetes patients who did not have any complications spent 6520 rupees ($134.9) for their diabetes care, while presence of three and above complications escalated the direct cost to 32,500 rupees ($672.6) per annum. The latest study by Viswanathan V et al. found that on an average, patients with foot complications (19020 rupees) and those who had two complications (17633 rupees) spent four times more and patients with renal disease (12690 rupees), cardiovascular (13135 rupees) and retinal complications (13922 rupees) spent three times more than patients without any complications (4493 rupees). This indicates the purpose for conducting this study. The main objectives of the study were to determine the average annual per patient direct cost for management of type 2 diabetes, to determine the average annual per patient direct cost for management of diabetic complications (foot ulcer, retinopathy, nephropathy, peripheral vascular disease), to analyze the factors affecting healthcare cost of diabetes and to determine the difference in Annual Medicine Cost (AMC), Annual Laboratory Cost (ALC), and Annual Consultation Cost (ACC) among non-complicated and complicated group.

MATERIALS AND METHODS
The study was conducted at department of diabetology, Kovai Medical Center and Hospital, an 800 bed multispeciality hospital in Coimbatore.

Study Design
It is a prospective observational study at Department of Diabetology and Endocrinology, Kovai Medical Center and Hospital, a multispeciality hospital in Coimbatore.

Study period
A period of 7 months from January 2013 to July 2013 in Kovai Medical Center and Hospital.

Inclusion criteria
1) Type 2 diabetes
2) Age ≥ 18 years
3) Hospitalized for complications like diabetic foot ulcer, nephropathy, nephropathy, peripheral vascular disease.

Exclusion criteria
1) Age below 18 years
2) Dialysis patients

Data collecting method
The study was conducted on the basis of patient perspective and is a type of prevalence based study. The medical history consisting of inpatient medical records were reviewed for the prescribed time period to record the patient's demographic characteristics, clinical status, duration of disease, length of stay, types of complications, cost details. The parameters such as the Annual Medicine Cost (AMC), Annual Laboratory Cost (ALC), and Annual Consultation Cost (ACC) were calculated for each patient. The total per patient direct cost per annum was calculated by the cost-of illness method. The direct cost was divided into three sub categories that include direct medical cost, direct non-medical cost and the management & monitoring cost. The average value of three sub categories was summed to calculate the total per patient direct cost per annum. The cost spend for patients having no complications, one complication, two complications, and three complications were also calculated by taking the average cost for total study population. The data was analyzed by Graphpad prism statistical software using unpaired t-test to find out whether there is any statistical difference in annual medicine cost, lab cost and consultation cost between the non-complicated and complicated group.

RESULTS AND DISCUSSION
A total of 120 type 2 diabetic patients were included in this study. The demographic details among the subjects reveal that 81(67.5%) were males while 39 (32.5%) were female (Table:1)

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>81</td>
<td>67.5</td>
</tr>
<tr>
<td>Female</td>
<td>39</td>
<td>32.5</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 1: Gender-wise distribution of patients
The factors affecting healthcare cost and hospitalization were the medicine cost, lab investigation cost, hospital admission cost, presence and severity of diabetes associated complications.

The statistical analysis unpaired t-test was performed to find out the difference in AMC, ALC, and ACC among the non-complicated group and complicated group.

P-value was found to be < 0.05 for AMC and ALC between non-complicated and complicated group which is significant. P value was found to be < 0.001 for ACC between non-complicated and complicated which is significant.

The study was conducted to determine the average per patient annual direct cost spent for the management of type 2 diabetes. In this study the socio-demographic factors such as the education, income, length of stay and the type of complications were found to be influencing the outcome of the diabetes and so the costs for treatment.

In the current study (N=120), among the gender wise prevalence there was a male predominance with 81 out of the total 120 patients and only 39 patients were female. These results reciprocates the result of the study conducted by Riewpaiboon A et al in which out of the total 475 study population 354 were females and only 121 patients were males.

The total average direct cost per annum for the management of type 2 diabetes was found to be 38589 rupees in this study. The patients who did not have any complications spent 15512 rupees as average direct cost per annum for their diabetes care, patients having one complication spent 25228 rupees as average direct cost per annum for their diabetes care, patients having two complications spent 30497 rupees as average direct cost per annum for diabetes care, patients having three complications spent 52607 rupees as average direct cost per annum for their diabetes care. These results reciprocates the results of the study conducted by Viswanathan V et al in which the total average direct cost per annum for the management of type 2 diabetes was found to be 25391 rupees, patients having no complications spent 6520 rupees as average direct cost per annum for their diabetes care, patients...
having one complication spend 9760 rupees as average direct cost per annum for their diabetes care, patients having two complications spent 15000 rupees as average direct cost per annum for their diabetes care, patients having three complications spent 32500 rupees as average direct cost for their diabetes care. The deviation in the respective costs may be due to the variation in the determinants of cost like the medicine cost, admission cost, lab cost and other investigation costs, consultation fee in the current study year(2013) with that of the study year (2009) of the reference study.3

The limitation of the study is that the indirect cost is not included in the study as it is difficult to determine the indirect cost for the study population where majority of them were unemployed and of the age group 51-60. The data obtained from the cost of illness analysis can be further used in the field of Cost Effectiveness and Cost Benefit analysis, methods more advanced and commonly employed while updating the drug formulary.

CONCLUSION

Diabetes is one of the major lifestyle diseases that can be a risk factor for several complications. The prevalence and the number of people living with diabetes in India is increasing every year, which imparts a burden on the economic growth.

Cost of illness studies can provide a framework for estimation of cost estimation for Cost Effectiveness and Cost Benefit Analysis, the methods which are commonly employed for decision making while updating the formulary. Pharmacist can perform his role when making formulary decisions as a member of Pharmacy and Therapeutic Committee (PTC), using the information gathered from pharmacoeconomic evaluation. Pharmacist can also give patient counselling on diabetes to patients as lack of proper knowledge about the disease is also a contributing factor towards the cost of care. A proper knowledge about the disease can contribute to proper monitoring of diabetes and thereby the extent of complications can be reduced.

Pharmacoeconomics is a less explored discipline in India. More education to healthcare professionals should be given to facilitate the use of pharmacoeconomic evaluation methods. Evidence based standard treatment guidelines and the proper implementation of Rational Drug Use would ensure better choice of therapeutic options. Factors affecting health-care costs and hospitalizations may help health-care providers intervene to improve patient management and possibly reduce health-care costs in the future. Most importantly a concerted effort is needed to reduce the incidence of diabetes mellitus in the society.

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A Comparative HRQOL Study of High Cost and Low Cost Anti-Diabetic Products

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ABSTRACT

Purpose: This study aims to compare high cost and low cost anti-diabetic products by a HRQOL study.

Methods: This is a cross-sectional, prospective, observational study carried out in a private endocrinology clinic which purchases medicines at a low cost and dispenses them free of cost to the patients. In the private out-patient clinic, medicines are prescribed by the doctor and purchased by patients. The patients purchase them from a pharmacy adjacent to the clinic and these medicines are comparatively of higher cost than the medicines given in a government hospital. The study group includes 117 randomly selected patients using anti-diabetic medicines of high cost and 115 randomly selected patients using low cost medicines. These patients were interviewed using SF-36, and their HRQOL values were recorded. The patients were counseled for three months by trained pharmacy students, with the help of printed brochures that explains the diet, dietary intake measures, dietary restrictions, daily exercise. At the end of three months, their HRQOL was recorded again.

Results: Pre-counseling, the low cost medicine users have a significantly lower mean HRQOL in all the domains and in total HRQOL, when compared to the high cost medicine users. The patient counseling effort has shown a significant improvement in the HRQOL values of all the domains of both high cost and low cost anti-diabetic medicines. However, the mean HRQOL values of the low cost medicine users were still significantly lesser than the high cost medicine users in most of the domains.

Conclusion: In general, users of low cost products of selected medicines showed a lesser HRQOL than the high cost products of the same medicines. Patient counseling resulted in improving the HRQOL values of all the patients in all the groups.

Keywords: Anti-diabetic drugs, HRQOL, Patient counseling, Quality of Life

INTRODUCTION

Prices of medicines influence patient compliance; they have an economic implication for the nation, as prices of medicines affect patient compliance which affects public health. Different nations have different regulatory systems for prices of medicines and differently structured markets. The number of formulations and bulk drugs manufacturing units in India has grown phenomenally in the last decade and the value of production including exports jumped from 10.0% to 15.0% for bulk drugs and 22.0% to 25.0% for formulations in 2009-2010.¹ The prices of the same medicine being formulated by different companies are widely different in the case of many medicines. This complex situation warrants a scientific investigation into the realities of medicines to find out whether there is any correlation between the prices of medicines on one hand and their effectiveness, as measured by the average HRQOL they impart, on the other hand.

Research into the quality of pharmaceutical products that are produced by several pharmaceutical companies has been going on for nearly a decade in the laboratories of AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam. The central idea was to verify whether the consumer could, with confidence, assume that all the products of a drug in the market are equivalent and interchangeable, because all companies in India are by law, required to release into the market, products that meet Pharmacopoeial requirements only. HRQOL is a good measure of the therapeutic efficacy of the drug. Diabetes causes a rise in blood glucose and this condition is very likely to adversely affect the physical, mental and social domains of the patients.
As the blood glucose is controlled by a therapy using an effective drug, this adverse effect is likely to be balanced and the HRQOL is expected to return to normal. Diabetes may cause the HRQOL to fall but the treatment of diabetes may cause the HRQOL to rise. Hence the capacity of different brands of the same generic, in whether they are causing proper blood glucose control or not is very likely to be reflected in the HRQOL of the patients using them.

This study was planned to find out whether there is any correlation between the costs of medicines and their effectiveness by carrying out a HRQOL study. This is a cross-sectional prospective observational study. Diabetic medicines are most widely used and their therapeutic effect is determined by clear clinical parameters such as blood glucose levels. There is a wide variation in costs of medicines being prescribed by doctors in endocrinology clinics and in government hospitals in the case of anti-diabetics. Research on HRQOL of diabetes patients was earlier undertaken in the laboratories of AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam. The hypothesis is that, though several factors affect HRQOL, the medicine being used is also a factor and is a significant factor. When the population being treated in a single clinic or hospital was surveyed for their HRQOL, it may be considered that all other factors are generally similar and the difference if any, in the HRQOL, due to the medicine must come out. In a study carried out by Vedavathi T the hypothesis taken was that if there is a significant difference between the therapeutic efficacy of branded generics and generics, then there should be a significant difference between the HRQOL levels of the patients who are using them over a long period. It was found that there is no significant difference between the HRQOL values of branded generic users and generic users and it was concluded that branded generic drugs and generic drugs result in equally good quality of life.

METHODS

Health related quality of life measures: standardized health related quality of life (HRQOL) measures are critical for a number of purposes, including evaluating the effectiveness of health care interventions for age related diseases. Over the years, the SF-36 has been used in surveys of general and specific populations, for comparing the relative burden of diseases across different sub-groups and in differentiating the health benefits produced by health care treatments. It was also used by the authors in previously reported work. SF-36 is a questionnaire which consists of questions concerning the patients assessment of his/her quality of life in eight domains, viz., PF-Physical Functioning, RP-Role Physical, BP-Bodily Pain, GH-General Health, VT-Vitality, SF-Social Functioning, RE-Role Emotional and MH-Mental Health. In the present research project, HRQOL values are measured to establish the correlation between the selected medicines of the same chemical compounds of high cost and low cost products taking the hypothesis that there is no significant difference between the mean HRQOL of patients using low cost anti-diabetic medicines and the mean HRQOL of patients using high cost products of same medicines.

PATIENT POPULATION SELECTION

This study was carried out at King George Hospital, Visakhapatnam, and in the outpatient clinic of an endocrinologist, Dr. A. Mythili, Associate Professor, Department of Endocrinology, Andhra Medical College. The patients attending the outpatient department of King George Hospital (KGH), Visakhapatnam are dispensed with low cost anti-diabetic medicines. The government selects/purchases the medicines after issuing the tenders for submission of quotations and then the quotation with the least prices is selected for purchase, after the pharmaceutical company fulfills the norms of the Government. There are four private outpatient clinics for endocrinology in Visakhapatnam and the outpatient clinic run by Dr. A. Mythili was selected for the study by a randomized procedure. The patients attending the outpatient clinic of Dr. A. Mythili are prescribed high cost medicines, available at the retail medical shops. The prescribed medicines are very high in cost compared to those dispensed in KGH. The high cost glibenclamide tablet is 23.20 times costlier than the low cost glibenclamide tablet and the high cost metformin HCI tablet is 8.93 times costlier than the low cost metformin HCl. This research work was approved by the Institutional Ethics Committee for Human Research of Andhra University as well as by the Superintendent of KGH, Visakhapatnam. The chosen instrument for the study of health related quality of life (HRQOL), was SF-36, whose copy right is owned by Quality Metric. License was obtained from Quality Metric after paying the relevant fee for SF-36, its English version, Telugu version (the local language), and its scoring manual.

SELECTION OF PATIENTS

The investigator waited in the outpatient area of the hospital or clinic and approached the patients whose number in the list of patients corresponded to a randomly identified digit or it's multiple. The investigator waited in the hospital and the clinic, during the outpatient department hours on a number of days and on each day, one digit between 2 and 10 was randomly identified and patients with that number or a multiple of that number were selected into the study. The patients who were on anti-diabetic medicines for more than one year, who were above fourteen years, who were attending the outpatient department in one of the two selected healthcare centers and who were willing to participate in the study were approached by the investigator with a request for
participation in the study. Those patients who accepted to participate were selected into the study. The researcher obtained a written informed consent and then administered the SF-36 questionnaire in English or in the regional language, Telugu, as the situation demanded. The patients were given the opportunity to fill the questionnaire themselves, but where they could not do it, the investigator filled the questionnaire after obtaining answers from them. Each interview lasted for about thirty minutes on an average. For each patient, quality of life (QOL) assessment was done when the patient was enlisted into the study and the second was done three months later. Counseling on the usage of medicines and requirements of diet restrictions and daily exercise was given to the patients in these three months, either by investigator or by trained IV B. Pharm students of Andhra University.

The objective in this study was to find out the HRQOL in a group of patients using a type (either low cost or high cost) of medicines, before and after patient counseling. This plan of work was implemented to obtain information which could help the investigator in establishing whether there is any significant difference between the HRQOL values of patients using low cost medicines and high cost medicines, whether there is any effect for patient counseling and whether the effect of treatment is consistent in both categories.

The questionnaires filled were given scores by the scoring manual for SF-36. The scores obtained in eight domains and the total QOL values were analyzed graphically and were compared by t-test.

RESULTS

The demographics of the patients who participated in the HRQOL study are shown in Table 1. The pre and post counseling results of the HRQOL values in the different domains and are shown in Figure 1 and in Tables 2 and 3.

DISCUSSION

Among the patients in KGH, 41 were male patients and 74...
were female patients. In both males and females, highest number of patients from the selected group of study was found to be in the age group of 50 to 59 years. Among the patients who attended the clinic 60 were males and 57 were females. Highest number of patients from the selected group of study was in the age group of 50 to 59 years in males and 30 to 39 years in females. Patients who attend private clinics are usually affluent people and one may infer from this observation that diabetes is occurring in affluent females at a younger age.

Figure 1 and Tables 2 and 3 indicate that, pre-counseling, the low cost medicine users have a lower mean HRQOL in all the domains and in total QOL. The mean HRQOL values of the patients using high cost anti-diabetic medicines are significantly different from those using low cost medicines, in all the domains and in total QOL. The variability of the mean HRQOL values is more in the patients using low cost anti-diabetic medicines than in those patients using high cost medicines. It is observed from the probability values that the difference is significant in all the domains of pre-counseling.

The bars in Figure 1 and the post counseling mean HRQOL values shown in Table 3, indicate a rise in height from the pre-counseling stage in all the domains and in total HRQOL. However, the bars of the low cost medicine users are still smaller than the bars of the high cost medicine users. The difference between the means of the two categories is significant in the post counseling HRQOL values in all domains but one and in total HRQOL. There is a reduction in the variability in all the standard deviation values indicating that patient counseling has affected a reduction in variability among patients with respect to their HRQOL. However, the variability in the low cost medicine users is still higher than those of high cost medicine users in all the domains and in total HRQOL. Based on these results, the null hypothesis of no significant difference was rejected and it was concluded that the difference between the two categories of patients, in the mean HRQOL values and their variability was significant.

Patient counseling resulted in improving the HRQOL values of all patients. The power of a test is defined as the probability of the test rejecting the null hypothesis when it is in fact false. The probability of deciding that the null hypothesis is true when it is actually false is the probability of a type II error. The

<table>
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<tr>
<th>S.No</th>
<th>Component</th>
<th>N</th>
<th>Mean</th>
<th>S.D</th>
<th>P-value</th>
<th>Decision</th>
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<tr>
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**P value:** S, significant if $P<0.01$  
NS, not significant if $P>0.05$
The power of a test is known as “one minus the probability of a type II error” or (1-β). The power values of the 't' test carried out to find the significance of the difference between high cost medicine users and low cost medicine users, given in Tables 2 and 3 indicate that in all cases the values are equal to one. This may be attributed to the large differences between the means and the big sizes of the samples. It may be said that the 'α' value used and the sizes of the samples were such that if there is a significant difference, it would certainly be detected in most of the cases.

Comparison with past work

Vijayaratna et al carried out a comparison of quality of life and improvement in blood pressure and blood glucose values of patients using branded generic and generic medicines for hypertensive and diabetes treatment. They concluded that there is no difference between the selected products of branded generic medicines and generic medicines. They found that there was good correlation between improvement in biochemical values and improvement in HRQOL (rank correlation coefficient between 0.8 and 1.0).

The present work differs in some experimental conditions from this previously reported work. The present work compares selected products of low cost drugs and high cost drugs. In the previous work the HRQOL values of branded generics were recorded from AU Health Center, Andhra University, Visakhapatnam and in the present work, the HRQOL values are recorded from an endocrinologist's outpatient clinic. It may be said that this difference might have resulted in the HRQOL values of low cost drugs coming out to be significantly lower than those of high cost drugs.

CONCLUSION

1. The mean HRQOL values of the patients using selected high cost anti-diabetic medicines are significantly higher than the corresponding values of users of low cost products of the same medicines.

2. Patient counseling resulted in improving the HRQOL values of all patients. But the difference between the two groups persisted, even after patient counseling.

REFERENCES:


Impact of Patient Education on Quality of Life of Asthma Patients in an Indian Tertiary Care Hospital

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ABSTRACT

Background: The overall burden of asthma in India is estimated at more than 15 million patients. It can place considerable limitations on the physical, emotional, social and professional lives of patients, with substantial negative impact on quality of life (QOL). Literature provides evidence that clinical pharmacists have contributed to patient care through education which enhances the feasibility of asthma self-management.

Objectives: To study the impact of patient education provided by the clinical pharmacist regarding asthma, self-management and inhaler technique in improving the quality of life of asthma patients in a South Indian tertiary care hospital.

Methodology: The study was randomized, comparative and intervention based with 92 patients who were randomized into intervention (49 patients) and control groups (43 patients). After the enrolment period of 1 month (Baseline), three follow-ups were carried out at the intervals of 1st, 3rd and 5th month. The parameters measured in this study included peak expiratory flow rate (PEFR), inhalation technique, QOL and asthma self-management. During the follow-ups, intervention group received verbal and written education on asthma and inhaler techniques for self-management along with routine medical consultation whereas, the control group received only routine medical consultation during the follow-ups and education on asthma at the end of the study.

Results: At the baseline, mean PEFR value was 186.78 mL/sec in intervention group and 187.26 mL/sec in control group. A significant difference was noted at 2nd (P=0.006) and 3rd (P=0.000) follow-up. Intervention group showed a significant improvement in inhalation technique at 2nd(P=0.000) and 3rd (P=0.000) follow-up. At the end of the study, QOL of patients in the intervention group improved compared to control group. Significant improvement (P=0.000) was noted in Asthma Self-Management Questionnaire (ASMQ) score in the intervention group.

Conclusion: Results of this study shows that clinical pharmacist’s educational interventions had a positive impact on the understanding and self-management of asthma patients which helps in improving their health and quality of life.

Key Words: Asthma, ASMQ, Patient education, Quality of Life, SF-36

INTRODUCTION

Asthma is a syndrome that is characterized by paroxysmal or persistent symptoms such as breathlessness, chest tightness, wheezing and cough. Inflammation and its resultant effects on airway structure are considered to be the main mechanisms leading to the development and persistence of asthma.¹

The prevalence of asthma increased steadily over the later part of the last century, first in the developed and then in the developing world. Current estimates suggest that asthma affects 300 million people worldwide and an additional 100 million persons will be diagnosed by 2025.² The overall burden of asthma in India is estimated at more than 15 million patients.¹ About one half of the cases develop before age 10 and another third develop before 40. Allergic asthma which accounts for 25% of the cases tends to be seasonal and occurs more commonly in children & young adults.³ Much of the day-to-day responsibility for managing asthma falls on the patient and the patient's family.¹ Patients with asthma similar to patients with other chronic diseases are poorly adherent to drug therapy. Asthma can place considerable limitations on the physical, emotional, social and professional lives of patients, with substantial negative impact on quality of life.⁶ These problems can be reduced through patient education by a pharmacist.⁷,⁹,¹⁰

Asthma education is considered an essential component of asthma management. It is necessary to help patients gain the motivation, skills and confidence to control their asthma.

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E-mail: ramjanshaik@gmail.com
Globally a poor level of practical knowledge and understanding of asthma has been reported among patients. In India, asthma patient education is not a routine practice and hence, teaching the patient to recognize and intervene in exacerbations during their earliest stages can be helpful in avoiding more serious morbidity and in some cases, mortality. Patient Education has been defined as “a planned learning experience using a combination of methods such as teaching, counseling, and behavior modification techniques which influence patients' knowledge and health behaviour ... (and) involves an interactive process which assists patients to participate actively in their health care.”

This study focuses on the evaluation of the impact of patient education provided by a clinical pharmacist regarding the disease, improving quality of life, inhalation technique and self-management for asthma patients in a South Indian tertiary care hospital.

METHODOLOGY

The study was a randomized, comparative, controlled intervention study carried out for a period of 9 months in the medicine out-patient department of a tertiary care hospital, in South India. Ethical committee clearance was obtained from the Institutional Ethical Review Board of the hospital. Written informed consent was obtained from the patients before enrolling them in the study.

Study criteria

Data such as demographics, history of illness, family history, personal habits, PEFR values, patient knowledge about the illness was collected from patient's out-patient department (OPD) cards, laboratory reports and by interviewing the patients. All out-patients diagnosed with varying degrees of severity of asthma in the medicine out-patient department with oral or inhaled medication and those who were willing to participate till the end were included in the study. Patients were included in the study with reference to the senior practicing physician of the hospital. Participating patients with co morbid conditions such as hypertension, diabetes mellitus, ischemic heart disease, anxiety, hypothyroidism, epilepsy and dyslipidemia. Pediatric patients and pregnant asthmatic women were excluded from the study.

Method of collection of data:

The patients were randomized into two groups; control and intervention using a chit method. Each patient chose a folded paper (called a “chit” in India) that stated “Intervention” or “Control” and based on what was selected, the patient was assigned to the respective group. Intervention group received comprehensive medication counseling, asthma education at regular intervals. The control group received routine medical consultation during the follow-ups and counseling at the end of the study. Medication counseling was divided into 3 phases:

(1) Pre-intervention phase

In this phase, the quality of life of patients was assessed by administering standardized asthma QOL questionnaire (SF-36). Asthma self management questionnaire (ASMQ) was used to assess their knowledge regarding self-management of disease. One-on-one interviews were conducted to document levels of self-reported adherence to therapy and life style pattern of patients such as level of exposure to allergens, pollution. Patients’ existing knowledge regarding the use of inhaler was checked by using standardized nine steps of inhalation technique as shown in table 1. Patients were evaluated for PEFR at entry into the study (baseline).

(2) Intervention phase

In the intervention phase, patients were educated about asthma and its management, its complications, the importance of adhering to medications, life style modifications with the help of one to one interview and by providing them with an information leaflet for asthma. The SF-36 survey was administered by the clinical pharmacist using the language which the individual patient can follow. Patients were also shown correct inhalation technique by using a placebo inhaler.

Patients were also evaluated for PEFR during the follow-up visit; 1st follow-up was after 1 month of baseline (entry) and 2nd as well as 3rd follow-ups at the interval of 2 months.

(3) Post-intervention phase

Patients were re-assessed at 3rd month (2nd follow-up) and 5th month (3rd follow-up) to determine the improvement in their QOL, by using SF-36 questionnaire. Patients were re-evaluated at 5th month to assess their knowledge regarding self-management of disease. Improvement in correct technique of inhaler was checked by using the nine-step inhalation technique. At the end of the study, control group patients were also educated about the self-management of the disease. (Table 1)

Data analysis

At the end of the study, statistical analysis was performed using SPSS. Baseline characteristics (gender, age, education) were analyzed using chi-square test. t-tests for independent samples were performed to compare the participants PEFR, Inhalation technique score, SF-36 scores and ASMQ scores. P-values <0.05 were considered statistically significant.

RESULTS

In a span of 1 month of the baseline study, 122 patients were identified by senior practicing physicians. These patients
were approached to participate in this study among whom 115 patients signed the consent form. However, only 108 patients participated in the 1st follow-up (end of 1st month of the study), followed by 97 patients in the second (3rd month of study) and 92 patients in the third follow-up (5th month of the study). 23 patients dropped out of the study due to factors like, distance, lack of continued interest. The remaining 92 patients completed the study and the data was included for final statistical analysis. Amongst study population, majority of the patients were found to be male in both intervention group 26 (53.1%) and control group 24 (55.8%), followed by female 23 (46.9%) in intervention and 19 (44.2%) in control groups. The minimum age group of the patients was between 20-25 years. The mean age in the intervention group was found to be 51.9±15 years ranged from 20 to >80 years and 52.7±15 years in the control group ranged from 20-79 years. Most of the patients 17(34.7%) were found to have education <4 years. Both groups were compared and no statistically significant difference with reference to gender, age and education level was found. The demographic characteristics of 92 patients is shown in Table 2.

**PEFR as a parameter of asthma control**

There was no statistically significant difference observed in PEFR of both the groups at baseline \((P=0.971)\). Mean PEFR value at baseline was 186.78 mL/sec in intervention group and 187.26 mL/sec in control group. By the 1st follow-up, improvement was observed in both the groups though no significant difference \((P=0.447)\) was evident. However, intervention group showed significant improvement in PEFR at 2nd \((P=0.006)\) and 3rd follow-ups \((P=0.000)\), whereas there was no improvement seen in the control group. The comparison of PEFR between the intervention and control groups at each follow-up is shown in Table 3.

**Inhalation technique**

At the baseline, both the groups did not show any significant difference in inhalation technique score with the mean inhalation technique score of 2 in intervention group and 1.81 in control group. By 1st follow-up, improvement was noted in the intervention group though it was not statistically significant \((P=0.447)\). A significant difference was noted at 2nd \((P=0.000)\) and 3rd \((P=0.000)\) follow-ups in intervention group compared to control group. Comparison of inhalation technique scores between intervention and control group at each follow-up is shown in table 4.

**Quality of life**

The SF-36 is a generic instrument to assess patient's health related quality of life. It generates a score ranging from 0 (worst possible health) to 100 (best possible health) for eight multi-item domains. Aggregate scores are compiled as a percentage of the total points possible, using the RAND scoring table. Scores from those questions that address each

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**Table 1: Inhaler Technique Checklist used in the study**

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<tr>
<th>Steps</th>
<th>Description</th>
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<td>1</td>
<td>Shake the inhaler thoroughly</td>
</tr>
<tr>
<td>2</td>
<td>Hold the inhaler upright</td>
</tr>
<tr>
<td>3</td>
<td>Exhale normally</td>
</tr>
<tr>
<td>4</td>
<td>Place mouthpiece in mouth, lips closed around mouthpiece</td>
</tr>
<tr>
<td>5</td>
<td>Activate canister while beginning slow inhalation</td>
</tr>
<tr>
<td>6</td>
<td>Continue to inhale slowly and deeply (for a count of 4)</td>
</tr>
<tr>
<td>7</td>
<td>Hold breath at full inspiration for a count of 5 to 10</td>
</tr>
<tr>
<td>8</td>
<td>Shake inhaler thoroughly between inhalation</td>
</tr>
<tr>
<td>9</td>
<td>Wait at least 1 minute (count of 60) between inhalations</td>
</tr>
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</table>

*Checklists based on previously published literature*

**Table 2: Demographic characteristics of study participants**

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<tr>
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<th>Control group</th>
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</tr>
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<td>Male</td>
<td>26 (53.1%)</td>
<td>24 (55.8%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Female</td>
<td>23 (46.9%)</td>
<td>19 (44.2%)</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uneducated</td>
<td>16 (32.7%)</td>
<td>10 (23.3%)</td>
<td>0.77</td>
</tr>
<tr>
<td>&lt; 4 years</td>
<td>17 (34.7%)</td>
<td>16 (37.2%)</td>
<td></td>
</tr>
<tr>
<td>4 – 10 years</td>
<td>12 (24.5%)</td>
<td>11 (25.5%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>4 (8.1%)</td>
<td>6 (14.0%)</td>
<td></td>
</tr>
</tbody>
</table>

*\(n = \) number of patients*

**Table 3: Comparison of PEFR between intervention and control group at each follow-up**

<table>
<thead>
<tr>
<th>Groups</th>
<th>(N)</th>
<th>Mean</th>
<th>SD</th>
<th>(T)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEFR value at baseline (mL/sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>49</td>
<td>186.78</td>
<td>69.214</td>
<td>-0.036</td>
<td>0.971</td>
</tr>
<tr>
<td>Control</td>
<td>43</td>
<td>187.26</td>
<td>56.174</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEFR value at 1st follow up (mL/sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>49</td>
<td>195.20</td>
<td>50.72</td>
<td>0.764</td>
<td>0.447</td>
</tr>
<tr>
<td>Control</td>
<td>43</td>
<td>180.70</td>
<td>56.152</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEFR value at 2nd follow up (mL/sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>49</td>
<td>237.86</td>
<td>61.813</td>
<td>4.618</td>
<td>0.006</td>
</tr>
<tr>
<td>Control</td>
<td>43</td>
<td>180.70</td>
<td>56.152</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEFR value at 3rd follow up (mL/sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>49</td>
<td>238.47</td>
<td>48.92</td>
<td>5.817</td>
<td>0.000</td>
</tr>
<tr>
<td>Control</td>
<td>43</td>
<td>175.35</td>
<td>55.17</td>
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<td></td>
</tr>
</tbody>
</table>

*\(N = \) number of patients*
specific area of functional health status are then averaged together, for a final score within each of the 8 dimensions measured. (e.g. pain, physical functioning etc.). Table 5 shows the comparison of SF-36 score between intervention and control group at the baseline, 2nd follow-up and 3rd follow-up. The results indicated that there was significant improvement in the quality of life of patients belonging to intervention group compared to control group.

**Asthma self-management**

The 16-item, multiple-choice asthma self-management questionnaire (ASMQ) was used. It generates a score of 0 to 100, with higher scores indicating more correct responses.

### Table 4: Mean of Inhalation technique score at different follow ups

<table>
<thead>
<tr>
<th>Domains</th>
<th>Groups</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhalation Technique Score at baseline</strong></td>
<td>Intervention</td>
<td>49</td>
<td>2.00</td>
<td>1.00</td>
<td>0.930</td>
<td>0.355</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>43</td>
<td>1.81</td>
<td>0.906</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inhalation Technique Score at 1st follow-up</strong></td>
<td>Intervention</td>
<td>49</td>
<td>4.45</td>
<td>1.50</td>
<td>0.764</td>
<td>0.447</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>43</td>
<td>1.86</td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inhalation Technique Score at 2nd follow-up</strong></td>
<td>Intervention</td>
<td>49</td>
<td>5.90</td>
<td>1.3731</td>
<td>5.976</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>43</td>
<td>1.86</td>
<td>0.990</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inhalation Technique Score at 3rd follow-up</strong></td>
<td>Intervention</td>
<td>49</td>
<td>7.76</td>
<td>1.13</td>
<td>26.460</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>43</td>
<td>1.91</td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*N=number of patients

### Table 4: Mean of Inhalation technique score at different follow ups

<table>
<thead>
<tr>
<th>Domains</th>
<th>Groups</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical functioning</strong></td>
<td>Baseline</td>
<td>Intervention</td>
<td>49</td>
<td>36.12</td>
<td>29.462</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>43</td>
<td>38.02</td>
<td>28.788</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2nd follow-up</td>
<td>Intervention</td>
<td>49</td>
<td>57.96</td>
<td>25.164</td>
<td>4.89</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>43</td>
<td>33.14</td>
<td>23.223</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3rd follow-up</td>
<td>Intervention</td>
<td>49</td>
<td>74.08</td>
<td>18.870</td>
<td>12.68</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>43</td>
<td>25.471</td>
<td>7.720</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Role, Physical**

| Baseline | Intervention | 49 | 28.06 | 41.026| 0.08 | 0.933|
| Control  | 43 | 27.44 | 27.611|      |      |
| 2nd follow-up | Intervention | 49 | 50.51 | 30.826| 4.87 | 0.000|
| Control  | 43 | 22.91 | 22.153|      |      |
| 3rd follow-up | Intervention | 49 | 64.59 | 26.410| 9.10 | 0.000|
| Control  | 43 | 18.95 | 20.920|      |      |

**Role, Emotional**

| Baseline | Intervention | 49 | 34.69 | 45.623| 0.17 | 0.864|
| Control  | 43 | 36.24 | 39.752|      |      |
| 2nd follow-up | Intervention | 49 | 42.86 | 44.618| 0.83 | 0.408|
| Control  | 43 | 35.46 | 40.134|      |      |
| 3rd follow-up | Intervention | 49 | 51.02 | 39.730| 2.57 | 0.012|
| Control  | 43 | 30.81 | 35.190|      |      |

**Energy/Fatigue**

| Baseline | Intervention | 49 | 36.48 | 20.097| 0.77 | 0.443|
| Control  | 43 | 39.42 | 15.923|      |      |
| 2nd follow-up | Intervention | 49 | 42.19 | 15.882| 2.04 | 0.045|
| Control  | 43 | 35.70 | 14.540|      |      |
| 3rd follow-up | Intervention | 49 | 46.68 | 17.470| 4.65 | 0.000|
| Control  | 43 | 30.93 | 14.610|      |      |

**Emotional well being**

| Baseline | Intervention | 49 | 51.37 | 25.237| 1.48 | 0.142|
| Control  | 43 | 58.86 | 22.953|      |      |
| 2nd follow-up | Intervention | 49 | 55.12 | 21.561| 0.12 | 0.902|
| Control  | 43 | 55.67 | 21.109|      |      |
| 3rd follow-up | Intervention | 49 | 59.16 | 17.950| 2.59 | 0.011|
| Control  | 43 | 53.40 | 21.050|      |      |

**Social functioning**

| Baseline | Intervention | 49 | 60.031| 25.400| 0.98 | 0.331|
| Control  | 43 | 65.593| 23.500|      |      |
| 2nd follow-up | Intervention | 49 | 64.500| 23.031| 0.03 | 0.977|
| Control  | 43 | 64.640| 24.055|      |      |
| 3rd follow-up | Intervention | 49 | 66.30 | 21.950| 0.43 | 0.667|
| Control  | 43 | 64.19 | 24.930|      |      |

**Body pain**

| Baseline | Intervention | 49 | 53.367| 24.878| 0.49 | 0.627|
| Control  | 43 | 50.655| 28.519|      |      |
| 2nd follow-up | Intervention | 49 | 57.245| 21.428| 1.59 | 0.116|
| Control  | 43 | 50.049| 22.024|      |      |
| 3rd follow-up | Intervention | 49 | 59.08 | 19.970| 1.26 | 0.112|
| Control  | 43 | 45.47 | 23.220|      |      |

**General health**

| Baseline | Intervention | 49 | 31.43 | 23.496| 0.98 | 0.331|
| Control  | 43 | 36.28 | 24.025|      |      |
| 2nd follow-up | Intervention | 49 | 50.82 | 25.132| 2.83 | 0.006|
| Control  | 43 | 36.28 | 24.025|      |      |
| 3rd follow-up | Intervention | 49 | 64.08 | 19.490| 7.92 | 0.000|
| Control  | 43 | 30.58 | 21.070|      |      |
At baseline, mean ASMQ score was 4.49 in intervention group and 3.91 in control group. Intervention group showed statistical improvement at the 3rd follow-up ($P=0.000$) compared to control group.

**DISCUSSION**

In many countries, clinical pharmacy services are still in their infancy, with pharmacists spending a predominant amount of time on distributive and manufacturing activities. In India, pharmacy practice is still in its infancy. The clinical pharmacist's contribution to patient care through education and counseling is an approach being advocated to optimize drug therapy and improve patients' quality of life. At the baseline of the present study, patients in both groups were found to have poor QOL. The observations showed significant improvement in PEFR of the intervention group. Previous studies involving patient education also demonstrate similar improvement in PEFR value of asthma patients.

| Table 6: Comparison of ASMQ scores between intervention and control groups |
|-----------------------------|-----------------------------|--------|--------|
|                             | Asthma self-management scores (Mean±SD) | t      | p      |
| Follow ups                  | Intervention                | Control|        |
| Baseline                    | 28.6±18.7645                | 24.395±15.5 | 1.146  | 0.255  |
| 3rd follow-up               | 75.13±16.06                 | 25.12±15.47 | 15.159 | 0.000  |

There is evidence that poor inhaler technique is associated with poor asthma control. The efficacy of asthma treatment depends on patients' ability to perform the inhalation technique correctly. Many studies have shown that education has a significant positive impact on the patients' knowledge of correct inhalation technique. This study also demonstrates that patient education facilitated by the clinical pharmacist resulted in the improvement of inhalation technique. However, one study showed no significant improvement, probably due to the short duration of the educational intervention and the lack of reinforcement in subsequent visits. Patient education showed statistically significant improvement ($P=0.000$) in most of the domains of SF-36 questionnaire except social functioning which is not related to asthma and body pain which is also not specifically related to asthma. This shows the impact of asthma education on their quality of life. However, one study reported that the intervention carried out by specialized asthma nurses in 41 general practices in London, did not detect any improvement in quality of life or in the quality of asthma care, probably due to the large number of patients who required management in primary care and the high turnover of practice nurses. Since inhalation medication is most important part of the treatment in asthma, improper use of the same leads to worsening of the condition. Most of the patients in both the groups were found to be using improper method for inhalers. At baseline, mean inhalation technique score was 2 in intervention group and 1.81 in control group. A significant difference was observed at 2nd ($P=0.000$) and 3rd ($P=0.000$) follow-ups. Education showed significant improvement in intervention group. Similar result was found in the study conducted by M Schulz et al., in which there was significant improvement with regard to inhalation technique and PEFR value.

Although, new medicines and evidence based guidelines have been developed in recent years, there has been no major change in asthma morbidity and mortality. Asthma continues to be incompletely managed with the drugs being prescribed with or without supervision. Appropriate management recommends appropriate medication, patient education, and a written action plan, ongoing monitoring, appropriate follow-up, and specialty referral where appropriate. Self-management skills should be developed through education of the patients about asthma and its appropriate treatment by health care professionals. Clinical pharmacists can educate patients by providing information about asthma medications and by demonstrating how to use inhaled medications and peak flow meters. They can help patients to understand their asthma management plan.

**CONCLUSION**

As the first study of this nature in this tertiary care hospital of South India, initiating educational intervention for asthma patients in this study achieved improvement in PEFR, knowledge regarding inhalation technique, self-management of asthma and QOL of the patients who were included in the intervention group. This study validates that clinical pharmacist's educational interventions impact health and quality of life of asthma patients, positively.

**LIMITATIONS**

1. Pulmonary function test of patients in both groups at each phase of the study could not be carried out due to financial constraints of patients. Because of insufficient data, PFT of patients could not be compared.
2. Specific questionnaires like Asthma Quality of Life Questionnaire (AQLQ [Juniper]) or (AQLQ [Marks]) could not be used in the study as required permissions could not be obtained within the limited study period.
3. In this study, QOL is based on self-reports of patients and has not been validated on any other objective assessments.
4. Patients were not available for follow-up and hence the exact reasons other than their lack of interest, could not be documented.
ACKNOWLEDGMENTS

We are thankful to the Management & Principal of Al-Ameen college of Pharmacy, Bangalore and Medical Superintendent of St. Martha's Hospital, Bangalore for their support. We also wish to thank all the Unit Heads of Medicine Department of the hospital and Mrs. Mahvash Iram, Lecturer, Department of Pharmacy Practice for their help during this study.

REFERENCES

Drug Utilization and Evaluation of Hmg-co a Reductase Inhibitors in Tertiary Care Teaching Hospital

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2Department of Pharmacy Practice, ISF College of Pharmacy, Ferozepur Road, Ghal Kalan, Moga, Punjab, Postal Code: 142001

ABSTRACT

A prospective study was conducted to evaluate the drug utilization of HMG-CoA reductase inhibitors (statins) in a tertiary care teaching hospital to ensure rational use, safety, prescribing pattern and economic strategy for 6 months, in which 440 patients prescribed with statins were recruited for the study and the data were collected and analyzed statistically. Statins were more prescribed in 60-70 years age group and it was prescribed mainly for primary and secondary prevention of cardiac and cerebro-vascular complications (62.87%) followed by dyslipidemia (29.38%) and hypertriglyceridemia (7.74%). Atorvastatin was more prescribed (85.42%) than Simvastatin (4.78%) and Rosuvastatin (9.79%). Drug-drug interactions were found with digoxin, verapamil and phenytoin. The DDD/12 bed days were found to be 82.32, 2.4, and 15 for the three statins respectively, the prescribed daily dose and the defined daily dose were as follows: Atorvastatin 19.33mg;20mg, Simvastatin 15.73mg;30mg, and for Rosuvastatin 15.73mg;10mg. The cost of the three statins according to the amount utilized was found to be 4918, 302 and 887 rupees respectively. The dosages used for Atorvastatin were generally closer to the maintenance dose recommended by WHO. Whereas a slight difference seen in case of Simvastatin and Rosuvastatin. Though several brands available the least priced statins brands can be selected rather than costlier brands which cause a drastic increase in patient's drug compliance as well as economic status.

INTRODUCTION

The World Health Organization (WHO) in 1997 defined drug utilization as the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences.1

Drug use is a complex process. In any country a large number of socio-cultural factors contribute to the ways drugs are used. In India, these include national drug policy, illiteracy, poverty, use of multiple health care systems, drug advertising and promotion, sale of prescription drugs without prescription, competition in the medical and pharmaceutical market place and limited availability of independent, unbiased drug information. The complexity of drug use means that optimal benefits of drug therapy in patient care may not be achieved because of underuse, overuse or misuse of drugs. Inappropriate drug use may also lead to increased cost of medical care, antimicrobial resistance, adverse effects and patient mortality.2

Studies on the process of drug utilization focus on the factors related to the prescribing, dispensing, administering, and taking of medication, and its associated events, covering the medical and non-medical determinants of drug utilization, the effects of drug utilization, as well as studies of how drug utilization relates to the effects of drug use, beneficial or adverse. The therapeutic practice is expected to be primarily based on evidence provided by pre marketing clinical trials, but complementary data from post marketing period are needed to provide an adequate basis for improving drug therapy.3

In recent years pharmacists have been increasingly involved in many emerging areas of pharmacy in addition to drug therapy. Pharmacists are expected to share their knowledge in improving policy decision in hospitals. At drug therapy level, pharmacists may utilize their expertise in making choice of drugs include or exclude in the formulary based on pharmacoeconomics.4

In recent years studies on drug utilization have become a potential tool to be used in the evaluation of health systems. The interest in drug utilization studies began in the early 1960s and its importance has increased since then because of increase in marketing of new drugs, wide variation in the pattern of drug prescribing and consumption, growing concern about delayed adverse effects and the increasing concern regarding the cost of drugs.5

The role of clinical pharmacists is to ensure rational, effective and safe treatment for the patient in their care. This involves interacting with patient to identify the medicines they have been taking before they were admitted to hospital and educating patient on the use of their medicines when they leave the hospital. Pharmacists, by virtue of their expertise...
and their mission of ensuring optimal patient outcomes, should work in the process of medicine use improvement through DUE. ⁶

Thus DUE plays a key role in helping the healthcare system to understand, interpret and improve the prescribing, administration and use of medications. The principal aim of DU research is to facilitate rational use of drugs, which implies the prescription of a well-documented drug in an optimal dose on the right indication, with correct information and at an affordable price. It also provides insight into the efficacy of drug use i.e. whether a certain drug therapy provides value for money. DU research can thus help to set priorities for the rational allocation of health care budgets. ⁷

STATINS

Statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin) competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme involved in cholesterol synthesis, especially in the liver. Statins are more effective than other lipid-regulating drugs at lowering LDL-cholesterol concentration but they are less effective than the fibrates in reducing triglyceride concentration. However, statins reduce cardiovascular disease events and total mortality irrespective of the initial cholesterol concentration. Statins should be considered for all patients, including the elderly, with symptomatic cardiovascular disease such as those with coronary heart disease (including history of angina or acute myocardial infarction), occlusive arterial disease (including peripheral vascular disease, non-hemorrhagic stroke, or transient ischemic attacks).

In patients with diabetes mellitus, the risk of developing cardiovascular disease depends on the duration and complications of diabetes, age, and concomitant risk factors. Statin therapy should be considered for all patients over 40 years with diabetes mellitus (type 1 and 2). In younger patients with diabetes, treatment with a statin should be considered if there is target-organ damage, poor glycemic control (HbA₁C greater than 9%), low HDL-cholesterol and raised triglyceride concentration, hypertension, or a family history of premature cardiovascular disease. Statins are also used for the prevention of cardiovascular disease events in asymptomatic individuals who are at increased risk. Statin treatment should also be considered if the total cholesterol concentration to HDL-cholesterol ratio exceeds ⁷

The recommendations of the NCEP for dyslipidemia control are aimed at decreasing or preventing cardiovascular disease attacks. In coronary heart disease (CHD) or in equivalent diseases, the target lipid levels are less than 100 mg/dl (2.6 mmol/l), which is called secondary prevention (NCEP, 2002). Patients with clinical CHD and the equivalent diseases have the following characteristics:

1. Clinical CHD: myocardial ischemia (angina), MI, coronary angioplasty, and/or stent placement, coronary bypass graft and prior unstable angina.
2. Carotid artery disease: stroke history, transient ischemic attack history, carotid stenosis > 50%.
3. Peripheral arterial disease
5. Diabetes mellitus.

If the patient does not have any of the above coronary heart diseases or equivalents, then he or she must be considered for primary prevention. This prevention is influenced by total cholesterol and HDL, age, gender, hypertension, family history of CHD, smoking, etc. All of these are considered as risk factors for cardiovascular diseases.⁸

METHODOLOGY

Study design: A prospective study was done for 6 months in which patient's data was collected from the hospital. Duration of the study was for 6 months which includes 440 subjects and the study was done under a multi-specialty tertiary care teaching hospital. Patient's identification was kept confidential and their medication chart was just reviewed according to their clinical condition.

Inclusion and exclusion criteria: Patients who are prescribed with HMG-CoA reductase inhibitors above age of 18 years. Pregnant women and breast feeding mothers were excluded from the study.

A specially designed proforma was prepared to collect data which includes patient demographics (age, sex, past medical history, past medication history, personal habits, and socio-economic status), drug details (name of the drug, dosage form, frequency, route of administration, duration of treatment) and medication profile.

Subjects fulfilling the inclusion criteria were recruited from the hospital. The subject's demographical data, physical examination, past medical history and medication history were recorded in the proforma. The drugs were categorized according to the ATC (anatomical therapeutic chemical) classification system. The collected data from the above sources were analyzed for:

Dosing pattern: Recommended dosages and dosing schedule followed for the statins that were prescribed.

Prescribed daily dose (PDD): It is defined as the average dose prescribed according to a representative sample of prescriptions. The PDD can be determined from prescription studies and medical or pharmacy records. PDD is useful in determining the average daily amount of a drug that is actually prescribed for a specific indication.
Defined daily dose (DDD): The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. It is useful in estimating the drug needs to provide a good therapeutic care to a patient.

Adverse drug reaction: Any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, long therapy of disease or for the modification of physiological function.

Drug interaction: Drug interaction is a situation in which substances affect the activity of a drug i.e., the effect are increased or decreased or produce a new effect that neither produce its own effect (Drug-drug/Drug-food/Drug-disease interactions).

Cost effectiveness: Cost-effectiveness analysis thus measures the incremental cost of achieving an incremental health benefit expressed as a particular health outcome that varies according to the indication for the drug.

The statistical analysis was performed using SPSS version 16 software and the results were analyzed by t-test and non-parametric test.

RESULT

This prospective study involved 440 patients. Among the patients 265 (60.2%) patients were male and 175 (39.8%) patients were female (Table 1 & Figure 1). The maximum number of the patients was found in the 66-75 year age group which was followed by age group 56-65 years -37.13%, 46-55 years-19.36%, 36-45 years-11.39%, above 75 years-7.74% and 26-35 years-2.28% (Table 2 & Figure 2). The specialty wise percentage of the patients prescribed with HMGCoAreductase inhibitors was highest in the cardiology department which accounts for 50.11% followed by neurology-21.87%, nephrology-10.25%, general medicine-7.52%, endocrine-4.33%, general surgery-2.05%, ortho-1.82%, urology-1.59%)and radiology- 0.46% (Table 3 & Figure 3). Statins prescribed in the population under study included atorvastatin, rosuvastatin and simvastatin of which the drugs were prescribed in 85.42%, 9.79% and 4.78% of the patients respectively (Table 4 & Figure 4).

Atorvastatin was prescribed in the hospital under different brand names which included Atorva (ZydusCadila)-29.8%, Tonaet (Lupin)-24%, Storvas (Stancare)-10.67%, Tonaet-TG (Lupin)-8.80%, Aztor (Sun Pharma)-4.8% , Atorlip(Cipla)-2.93%, Caat (Piramal Healthcare)-2.67%, Stator (Nicolas Piramal)-0.8%, S tatix (Biocon)-0.8%, Atorva-EZ (ZydusCadila)-0.53% (Table 5 & Figure 5).

Rosuvastatin was prescribed under brand names Rosuvas (Ranbaxy)-73.81% and Crestor (Astrazeneca)-26.19% (Table 6 & figure 6). Similarly Simvastatin was prescribed as Simvotin(Ranbaxy)-61.90%, Simcard (Cipla)-38.10%(Table 7 & Figure 7).
### Table 3: Specialty Wise Distribution Of Statins

<table>
<thead>
<tr>
<th>Department</th>
<th>No. of Patients (n=440)</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
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<td>Cardiology</td>
<td>221</td>
<td>50.11%</td>
</tr>
<tr>
<td>Neurology</td>
<td>96</td>
<td>21.87%</td>
</tr>
<tr>
<td>Nephrology</td>
<td>45</td>
<td>10.25%</td>
</tr>
<tr>
<td>General medicine</td>
<td>33</td>
<td>7.52%</td>
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<tr>
<td>Endocrinology</td>
<td>19</td>
<td>4.33%</td>
</tr>
<tr>
<td>General surgery</td>
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<td>2.05%</td>
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<tr>
<td>Urology</td>
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<td>1.59%</td>
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<td>Ortho</td>
<td>8</td>
<td>1.82%</td>
</tr>
<tr>
<td>Radiology</td>
<td>2</td>
<td>0.46%</td>
</tr>
</tbody>
</table>

Table 3 indicates the number of patients prescribed specialty wise. The highest number of patients of about 50.11% (221 patients) were found in cardiology. (P-value <0.05)

### Table 4: Statins Prescribed in Study Population

<table>
<thead>
<tr>
<th>Statins</th>
<th>No. of Patients (n=440)</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>376</td>
<td>85.42%</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>43</td>
<td>9.79%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>21</td>
<td>4.78%</td>
</tr>
</tbody>
</table>

Table 4 shows that among the statins prescribed in the study population atorvastatin was found to be the most common in 85.42% of patients followed by 9.79% of rosuvastatin and 4.78% of simvastatin. (P-value<0.05)

### Table 5: Brand Wise Distribution Of Atorvastatin

<table>
<thead>
<tr>
<th>Brands</th>
<th>No. of Patients (n=440)</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorva(ZydusCadila)</td>
<td>113</td>
<td>29.87%</td>
</tr>
<tr>
<td>Tonact (Lupin)</td>
<td>90</td>
<td>24.00%</td>
</tr>
<tr>
<td>Xtor (Ipca)</td>
<td>52</td>
<td>13.87%</td>
</tr>
<tr>
<td>Storvas(Stancare)</td>
<td>40</td>
<td>10.67%</td>
</tr>
<tr>
<td>Tonact-TG(Lupin)</td>
<td>33</td>
<td>8.00%</td>
</tr>
<tr>
<td>Aztor(Sun Pharma)</td>
<td>18</td>
<td>4.00%</td>
</tr>
<tr>
<td>Atorlip(Cipla)</td>
<td>12</td>
<td>2.93%</td>
</tr>
<tr>
<td>Caat (Piramal Healthcare)</td>
<td>10</td>
<td>2.67%</td>
</tr>
<tr>
<td>Stator(Nicolas Piramal)</td>
<td>3</td>
<td>0.80%</td>
</tr>
<tr>
<td>Statix (Biocon)</td>
<td>3</td>
<td>0.80%</td>
</tr>
<tr>
<td>Atorva-EZ (ZydusCadila)</td>
<td>2</td>
<td>0.53%</td>
</tr>
</tbody>
</table>

Table 5 shows the study population among various brands of atorvastatin prescribed in which atorva (29.87%) and tonact (24.00%) were found to be commonest prescribed. (p-value<0.05)

### Table 6: Brand Wise Distribution of Rosuvastatin

<table>
<thead>
<tr>
<th>Brand</th>
<th>No. of Patients (n=440)</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crestor(AstraZeneca)</td>
<td>11</td>
<td>26.19%</td>
</tr>
<tr>
<td>Rosuvas(Ranbaxy)</td>
<td>31</td>
<td>73.81%</td>
</tr>
</tbody>
</table>

TABLE 6 shows the study population among various brands of Rosuvastatin prescribed in which rosuvas (73.81%) was found to be prescribed more.
Among the patients under study, statins were prescribed for primary and secondary prevention of CHD and CVD in 277 patients (62.87%), Hyperlipidemia in 129 patients (29.38%) and Hyperlipemia in 34 patients (7.74%) -table 8 and figure 8.

Statins were prescribed under the strengths of 10 mg, 20 mg, 40 mg and 80 mg depending on the severity of the disease. Among 213 (48.52%) patients 10 mg atorvastatin was prescribed which was followed by 20 mg-70(15.95%) patients, 40 mg-91 (20.73%) and 80mg in 1(0.23%) patient. Similarly in case of rosuvastatin, the drug was prescribed 10mg among 18 (4.10%) patients and 20 mg among 24 (5.47%) patients. Simvastatin 10 mg was prescribed among 12 (2.73%) patients followed by 20 mg among 12 (2.05%) patients (Table 9 and Figure 9).

During the study a few possible drug-drug interactions were also observed. Major possible interactions caused by verapamil (calcium channel blocker) were observed in 10 (2.28%) prescription and moderate interactions caused by digoxin and phenytoin was seen in 84 (19.13%) prescriptions (Table 10, Figure 10) without causing any harm to the patients. Total defined daily dose (DDD) and cost of total defined daily dose (DD) of various dose strength of atorvastatin, simvastatin and rosuvastatin has been shown in table no. 11, 12 and 13 respectively.

Costs of prescribed brands of statins (per tablet) have been indicated in table no.14.

Table 15 indicates the use of ATC/DDD methodology as developed by WHO DUR group. The DDD/1000 /day was
found to be 6.88(82.59%) doses for atorvastatin, 0.2(2.40%) doses for Simvastatin and 1.25(15%) for Rosuvastatin. The DDD/12 bed days were found to be 82.32, 2.4, and 15 for the three statins respectively. The prescribed daily dose and the defined daily dose were as follows atorvastatin 19.33mg;20mg, Simvastatin 15.73mg;30mg, and for Rosuvastatin 15.73mg;10mg. The cost of the three statins according to the amount utilized was found to be 4918,302 and 887 rupees respectively.

**DISCUSSION**

The role of a pharmacist in clinical settings has undergone a revolutionary change. Today a pharmacist is not confined to the task of dispensing medicines only, but shoulders the responsibility in the mission of providing drug therapy to a patient in order to alleviate/cure illness. Pharmacists are trained to provide specialist services- health screening, diabetes care, immunizations, patient education on disease and medicines, nutrition, anticoagulation, chemotherapy and many more. Pharmacists are trained in the basic principles of drug education. This includes acquiring and understanding
drug information, focus on drug use problems, drug utilization reviews, verbal skills in patients counseling, etc.,. These skills are acquired with the objective of providing optimal patient care.

As statins are heavily used in this large corporate 1765 bedded hospital, this short term study was done to give an insight of utilization of statins in our hospital. Several studies have shown the incidence of an increase in usage of statins.7,9, 10, 11, 12, 13, 14

Patient who were prescribed statins have the presence of established hyperlipidemia, stroke, diabetes, cardiovascular disorders, which indicates the essential need for statin therapy as per national cholesterol education program (NCEP) adult treatment panel (ATP) III5.

Our study has generated data on optimal use of statins and we find that statins have been prescribed from age ranging 26 to 85 years with most patients in the 60 – 70 age group. Prescribing for statins has shown a gradual increase with an increase in the age of the patients and declined with age >75 years, indicating the prevalence of high morbidity in the 60 – 70 age group.

Atorvastatin (atorva, tonact) was the most prescribed statin in the study and though 10 mg was prescribed to more number of patients (48.52%) the PDD (prescribed daily dose) in the total population of 440 patients was found to be 19.33mg. WHO5 has recommended a DDD of 20mg and our usage is in accordance. Prescription data on the utilization of statins is expressed as DDD/1000 patients/day. It is only an average assumed maintenance dose but the prescribed daily dose differs from the defined daily dose as it is based on individual patient characteristics. This indicates our cautious use of statins.

The DDD/12 beds days were calculated according to WHO5 recommended and it was found to be 82.32 for Atorvastatin, 2.4 for simvastatin and 15 for Rosuvastatin. This indicates that 82.32% of statin users might receive a DDD of Atorvastatin in our hospital, but only 2.4% and 15% of statin users might receive simvastatin and Rosuvastatin respectively.

Though there are several equivalent statins the pricing for the different brands vary greatly, Simvastatin though low priced is less prescribed has Atorvastatin is preferred because of its better effectiveness and since Rosuvastatin is costlier it is less prescribed.

Similar studies also referred to support the study15-42

CONCLUSION

The study clearly indicates that HMG-CoA reductase inhibitors (statins) were used within locally and internationally accepted dosage ranges. The dosages used for Atorvastatin were generally closer to the maintenance dose recommended by WHO. Whereas, a slight difference seen in case of Simvastatin and Rosuvastatin.

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Analysis of Prevalence, Risk Factor and Pharmacotherapy of Hypertension in Outpatients

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ABSTRACT

OBJECTIVES: To determine the prevalence, risk factors and the pattern of prescribing of antihypertensives in Abha. METHODS: A survey of prevalence and prescribing pattern in patient with hypertension in primary care centres (Ballasmer General Hospital and Muhail General Hospital) of Abha, Kingdom of Saudi Arabia was conducted. RESULTS: The data was collected from 2228 subjects and females constitute 53.09% of the population and the prevalence of hypertension was 64% in females (n=757) and 49.5% in males (n=517). Comorbidities were reported in 1274 patients including ischemic heart disease (27.2%), heart failure (10.2%), diabetes (21%) and hyperlipidemia (27.3%). Patients on mono therapy were treated with β-blockers (9% Vs 0 %), calcium channel blockers (0% Vs 10%), angiotensin-converting enzyme inhibitors (27.3% Vs 15%), and angiotensin II receptor blockers (0 % Vs 15%), diuretics (36.4% Vs 5%) and combination drug therapy (use of ≥ 2 antihypertensive drug classes) was highest in the Muhail General Hospital (55% Vs 27.3% in Ballasmer General Hospital). CONCLUSIONS: In conclusion it is evident from our study that hypertension is a common public health problem in Abha of Saudi Arabia, and is still on the rise and the pharmacotherapy of hypertension in patients in both hospitals were found in some instances not to conform to recommended guidelines and this warrant urgent attention along with modifiable risk factors such as physical activity and obesity to prevent hypertension.

KEYWORDS: Hypertension, prevalence, risk factors

INTRODUCTION

Hypertension (HTN) and other related complications are recognized as emerging clinical and public health problems in Saudi Arabia.1 The global economic burden of increased blood pressure was estimated to consume US$370 billion worldwide and 10% of healthcare expenditures.2 It is the leading cause of cardiovascular disease worldwide.3 Although the condition is common, readily detectable, and easily treatable, it is usually asymptomatic and often leads to lethal complications if left untreated.4 Poorly controlled hypertension is a common finding in the outpatient setting.5 The reasons for poor control have not been clearly delineated, but attention has focused primarily on patient factors such as poor compliance with treatment and lack of access to care.6 Poor control of hypertension is associated with higher drug costs and more physician visits.7 Therefore the purpose of this study was to evaluate and compare therapeutic plan in outpatients with hypertension at Ballasmer General Hospital and Muhail General Hospital and determine the prevalence in both the genders between the age of 30 to 90 Years in the Asir Province.

SUBJECTS & METHODS

The data was collected from 2228 subjects during 2012-2013 from the medical records with evidence and previous history of hypertension for the study in the outpatient wards of the hospitals. We examined the patient's characteristics such as age, sex and comorbid conditions. Subsequently, we examined cross-hospital differences in the use of 7 antihypertensive drug classes (diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers,) and combination drug therapy (use of ≥ 2 antihypertensive drug classes). For a combination drug with multiple ingredients, each ingredient was treated as a separate drug.

STATISTICS

Only descriptive statistics are reported (means with 95% confidence intervals). Further analysis was inappropriate.

RESULTS

Description of study subjects:

Table 1 gives a breakdown of the sample characteristics, there are more female than male (46.90 % Vs 53.09 %). Most subjects were aged above > 60 years (46%), 36% were between 40-50 years and 18 % were aged 30 -40 years.

Hypertension prevalence:

The prevalence of hypertension was predominant in women (n=757) (women 64%, men 49.5% n=517). The prevalence of hypertension increased with age.

Prevalence of comorbidities of hypertension:

As shown in table 2 comorbidities were reported in 1274 patients including ischemic heart disease (27.2%), heart failure (10.2%), diabetes (21%) and hyperlipidemia (27.3%). Patients on mono therapy were treated with β-blockers (9% Vs 0 %), calcium channel blockers (0% Vs 10%), angiotensin-converting enzyme inhibitors (27.3% Vs 15%), and angiotensin II receptor blockers (0 % Vs 15%), diuretics (36.4% Vs 5%) and combination drug therapy (use of ≥ 2 antihypertensive drug classes) was highest in the Muhail General Hospital (55% Vs 27.3% in Ballasmer General Hospital).
patients including ischemic heart disease (27.2%), heart failure (10.2%), diabetes (21%) and hyperlipidemia (27.3%).

**Treatment Pattern:**

The use of all the five antihypertensive drug classes varied considerably in both the hospitals, especially for β-blockers (9% Vs 0%), calcium channel blockers (0% Vs 10%), angiotensin-converting enzyme inhibitors (27.3% Vs 15%), and angiotensin II receptor blockers (0% Vs 15%), diuretics (36.4% Vs 5%). Finally, the use of combination drug therapy (use of ≥ 2 antihypertensive drug classes) was highest in the Muhail General Hospital (55% Vs 27.3% in Ballasmer General Hospital).

**DISCUSSION**

This study documents the high prevalence of both hypertension and their association with other metabolic and cardiovascular risk factors, in a semi urban population of Abha. The prevalence of hypertension is increasing in Saudi Arabia affecting more than one fourth of the adult Saudi population. High prevalence of hypertension in males (49.5%) and females (64%) in the current study, confirms this increasing trend. This may also due to fact that people living at high altitude had a significantly higher risk of developing hypertension compared to those living at sea level. Furthermore lifestyle changes particularly eating habits, lack of physical inactivity, sedentary lifestyle are important contributors for development of atherogenic risk factors including hypertension, coronary heart disease and obesity.

In the current study, the prevalence of hypertension increased significantly from age group 30-40 to ≥ 60 years and is in agreement with the previous studies. Though the figures about the prevalence of hypertension in female are more than males, in the study, it may be due to the fact that women menopause is characterized by increases in blood pressure. It is evident from the study that comorbidities were associated with hypertension in our subjects. HTN and DM tend to coexist, and it expected that uncontrolled DM may lead to microvascular complications including arterial stenosis and hence elevated blood pressure. It is also plausible to expect DM to result from uncontrolled HTN since this could result in end organ damage involving the renal system and liver. Hypertension is the most common risk factor for HF, and it contributed a large proportion of heart failure cases in population-based studies. Hypertension and hyperlipidemia existence together in 27.3% of the patients in our study, further confirms the well-established fact that they are partially overlapping risk factors for cardiovascular disease. Studies have indicated increased death rates among patients with a history of hypertension, where ischemic heart disease may be more common than in the general population. Prescription patterns differ regionally. We have demonstrated that in BGH, diuretics were most prescribed medication for hypertension. However in MGH patients received ACE inhibitors and angiotensin receptor blocker frequently. ALLHAT (antihypertensive and lipid lowering treatment to prevent heart attack trial) study say diuretics are as effective as other, more expensive options for treating hypertension and should be used as the first line treatment. Interestingly, the parallel situation for ACE inhibitors in younger patients did not deter the British report from recommending them as first choice. It was further noted in our study that the use of β-blockers at MGH was absolutely nil and this is in compliance with the recommendation of SHMS report which states that β-blockers are no longer recommended as first-line therapy in patients over 60 years of age with uncomplicated HTN, because of the recently described trend toward worse outcomes in patients treated with β-blockers compared with those treated with other classes of antihypertensive drugs and increased risk of developing DM. The use of calcium channel blockers and angiotensin receptor blockers was evident at MGH when compared to BGH. Though the treatment pattern with monotherapy in both the hospitals were of varying pattern; however in the use of combination therapy they were consistent with the current guidelines suggestions for consideration of combination therapy for patients with stage 2 hypertension. Reports have indicated fixed-dose combinations offer many advantages such as increased compliance, convenience of use, additive or synergistic effects, and reduction of adverse events. Since we do not know the cause of the blood pressure elevation, therapy is essentially blind and a shotgun approach may be more efficacious than targeted therapy. This is particularly true because monotherapy invariably triggers a variety of counter regulatory mechanisms which are mitigated by combination therapy. The combination therapy has also been shown to have a renoprotective action superior to monotherapy, and beneficial metabolic effects, which led the European Society of Hypertension and the European Society of Cardiology guidelines ESHCG to recommend this association in patients at high risk for developing diabetes, who require combination therapy to reach the therapeutic goals.

<table>
<thead>
<tr>
<th>Table 1: Characteristics of population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristic</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>
Pregabalin induced Amnesia – A Case Report

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Professor, Department of Pharmacy Practice, JSS College of Pharmacy, SS Nagar, Mysore -15, India

INTRODUCTION

Pregabalin or S-(+)-3-isobutyrgaba is chemically (S)-3-aminomethyl-5-methyl hexanoic acid and is a structural and lipophilic analogue of Gama Amino Butyric Acid (GABA) substituted at 3-position to assist its diffusion across the blood-brain barrier. Although pregabalin is a structural analogue to GABA, it is inactive at GABA receptors and does not appear to mimic GABA physiologically. It is a potent ligand for the alpha-2-delta subunit of voltage-gated calcium channels inside the central nervous system. Food and Drugs Administration (FDA) has approved Pregabalin for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN), post herpetic neuralgia (PHN), adjunctive therapy for adult patients with partial onset of seizures, fibromyalgia, and neuropathic pain associated with spinal cord injury.

Adverse effect profile observed during controlled clinical trials with Pregabalin 75 mg/day is reported to cause dizziness, abnormal thinking, somnolence, tremor, confusion, twitching, dry mouth, speech disorder, cognitive changes, sedation, peripheral edema, increased appetite, weight gain, blurred vision and headache.

CASE REPORT

A 74 year-old male ambulatory patient suffering from type 2 diabetes mellitus and hypertension since 17 years and was on atenolol 25mg, simvastatin 10mg, alprazolam 0.25mg from last four years and well controlled. Five months ago, he was diagnosed to have herpetic neuralgia and treated with Pregabalin 75 mg and Methylcobalamine 750 µg to control his neuropathic pain. After 2 months of treatment, patient's wife observed symptoms of forgetfulness in the patient such as keeping his belongings in one place and searching in another place. Immediately she reported to the doctor about this observation. Causality assessment of the event with WHO and Naranjo' scales suggest “Possible”. However, exact mechanism of pregabalin induced amnesia is unclear. Severity of this reaction was at level-3 as per modified Hartwig and Siegel scale. This reaction found predictable, but not preventable in nature.

DISCUSSION

This is a case of an iatrogenic amnesia. The impact of drugs on memory disorders is particularly pronounced in elderly individuals due to poly pharmacy. It is established that there is a decrease of mnesic abilities with ageing; however iatrogenic influence cannot be ruled out when memory alteration occurs suddenly and/or recently in an elderly person without other symptoms of dementia.

The action of drugs on memory is more or less specific and serious depending on the memory system affected. Thus, analysis of the type of memory alteration can be used to inculpate a particular drug during poly pharmacy. Memory loss is an unusual forgetfulness and is mainly caused due to medicines such as benzodiazepines, anticonvulsants, antiepileptics, anticholinergic agents, isotretinoin, cyclosporin, and selective serotonin reuptake inhibitors.

Manifestations of memory loss include forgetting the location of spectacles, pens, towels which they have kept, phone numbers, and bank account number. The patient did not present these symptoms prior to receiving of pregabalin. Causality assessment of the event with WHO and Naranjo' scales suggest “Possible”. However exact mechanism of pregabalin induced amnesia is unclear. Severity was assessed...
by using Modified Hartwig and Siegel scale and found the severity is at level-3. This reaction is predictable, but not preventable in nature.  

In controlled clinical trials, pregabalin induced amnesia was reported with the use of pregabalin at a dose ranging from 150 mg to 600 mg/day for the management of neuropathic pain associated with diabetes, post herpetic neuralgia, fibromyalgia, and epilepsy.

In a French pharmacovigilance database of nine year period starting from January 2000 to December 2009, only seven case reports with pregabalin induced amnesia were reported. Among them only two reports were seen in the patients with more than 75 years of age suggesting that age has limited association in developing amnesia. Causes like medications in poly pharmacy may not be ruled out. In a case report of 75 year old patient, pregabalin had shown an association of inducing confusion and symptoms were resolved after de-challenging pregabalin.

In this patient, amnesia manifestations were observed only after taking pregabalin. After dechallenge, patient reported improved mnesic abilities confirming the association of Amnesia with Pregabalin.

CONCLUSION

FDA had reported very few cases of pregabalin induced amnesia in controlled clinical trials. However, this is the first case report observed in a patient who developed amnesia following pregabalin use.

ACKNOWLEDGMENT

We express our sincere thanks to Head, Department of Pharmacy Practice, Principal, JSS College of Pharmacy, Mysore and JSS University for academic support.

REFERENCES

Deterioration of Glycemic Control Induced by Pentoxifylline and Cilostazol in a Diabetic Patient with Peripheral Vascular Disease

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ABSTRACT

A 67-year-old South Asian male with type 2 diabetes mellitus, hypertension and ischemic heart disease was admitted with dry gangrene of right leg second toe. Angiography of right lower limb revealed peripheral vascular disease. He received pentoxifylline 400mg twice a day and cilostazol 100mg twice a day for 6 days following disarticulation. During this period, there was a marked elevation of blood sugar requiring higher dosage of insulin. On withholding the offending drugs there was a definite fall in blood sugar indicating a positive dechallenge. An erroneous exposure of pentoxifylline occurred following which the glycemic control further deteriorated, suggestive of a positive rechallenge though it was unintentional. Pentoxifylline and Cilostazol might have induced hyperglycemia by favoring intestinal glucose absorption through increased cAMP levels and GLUT2 expression necessitating management with higher dosage of insulin.

Keywords: Cilostazol, Diabetes mellitus, Hyperglycemia, Pentoxifylline

INTRODUCTION

Pentoxifylline is a non-selective phosphodiesterase inhibitor and cilostazol a selective phosphodiesterase-III inhibitor. In peripheral vascular disease, the therapeutic dose is pentoxifylline 400mg b.i.d. and cilostazol 50 – 100mg b.i.d. The frequent adverse events (AE) reported with pentoxifylline are nausea, anemia, fatigue and hypotension. The frequent AEs with cilostazol are pyrexia, anemia, pneumonia and diarrhea. As per FDA adverse event reporting system, the incidence of increased blood glucose with pentoxifylline is 0.41% and cilostazol is 0.27%.1,2,3,4 Drug induced hyperglycemia is mentioned for cilostazol by pharmaceutical companies in their summary of product characteristics.

CASE DESCRIPTION

This is patient with known case of type 2 diabetes mellitus for the past 20 years and ischemic heart disease. He was treated with glyclazide 80mg + metformin 500mg (1 ½ b.i.d), voglibose 0.3mg (1 t.i.d), insulin 70/30, aspirin 75mg + atorvastatin 10mg, metoprolol 50mg and telmisartan 40mg + amlodipine 5mg, and Insulin had been stopped a few days ago before admission due to an episode of hypoglycemia. He presented with swelling of right lower limb with discharge, pain, fever and blackish discoloration following thorn injury to the second toe 20 days ago. He was treated elsewhere with linezolid. His general and systemic examination was normal. Local examination revealed dry gangrene of the second toe of the right lower limb with cellulites of the plantar aspect of the sole.

Investigations revealed random blood glucose 66mg/dl (70 – 140mg/dl), glycosylated hemoglobin 9.8% (3.8 - 6.3%), haemoglobin 8.9g/dl (13-17g/dl), serum creatinine 1.8mg/dl (0.8-1.44 mg/dl), serum potassium 7.32meq/l (3.5 - 4.5 meq/l). Urine for ketones was negative. Angiography of right lower limb was suggestive of peripheral vascular disease. He underwent a minor surgery for disarticulation of the toe on day 2.

The patient had a mean glycemic level of 276mg/dl prior to therapy with phosphodiesterase inhibitors (day 3 to day 6) requiring an average of 18.5 Units insulin per day. On day 7 to day 12, during treatment with pentoxifylline 400mg (1 b.i.d) and cilostazol 100mg (1 b.i.d) , the mean blood glucose level was 351mg/dl, requiring higher dosage of insulin, a range of 28 to 95 Units of insulin. So, pentoxifylline 400mg (1 b.i.d) and cilostazol 100mg (1 b.i.d) were withheld. A significant fall in blood glucose with a mean blood glucose of 191mg/dl was then recorded, which was in-turn managed with an average of 69 Units insulin per day. An unintentional rechallenge with a single dose of 400mg pentoxifylline occurred on day 16 due to an administration error causing a
rise in the mean blood glucose to 275mg/dl requiring 84 Units insulin. This was followed by a positive dechallenge again on stopping the drugs. The glycemic level was brought under control with an average of 35.6 Units insulin per day. He was treated with glyclazide 80 mg + metformin 500 mg (1½ b.i.d), voglibose 0.3 mg (1 t.i.d), insulin (30/70) 20 Units – 0–10 Units, aspirin 75 mg + atorvastatin 10 mg (1 HS), metoprolol 50 mg (once daily) and telmisartan 40 mg + amlodipine 5 mg (1 HS), pentoxifylline 400 mg (1 b.i.d) and cilostazol 100 mg (1 b.i.d). The patient was suspected to have drug induced hyperkalemia due to telmisartan, which was later withheld and serum potassium was brought to 3.96 meq/l with calcium polystyrene sulfonate.

**DISCUSSION**

Drug induced hyperglycemia can have perpetual effects on the body, particularly in patients with diabetes. The present case is remarkable for the early diagnosis, aggressive management, twice positive dechallenge and a positive rechallenge. Following intake of pentoxifylline 400 mg b.i.d and cilostazol 100 mg b.i.d, there was a marked rise in the mean blood glucose level to 351 mg/dl which is about 1.3% increase in the baseline value. The patient at baseline had a high blood glucose value (276 mg/dl) which could have been contributed by the focal dry gangrene, sepsis and uncontrolled diabetes. However following disarticulation, he had a healthy wound and diet was strictly monitored as part of the in-patient care. Despite this, the patient's blood sugar continued to increase and the insulin requirement hiked progressively. The clinical situation raised the probability of drug induced hyperglycemia by phosphodiesterase inhibitors, i.e. pentoxifylline and cilostazol. None of the concomitant medications are known to cause hyperglycemia.

In the present case, there is a reasonable time relationship displayed by a marked elevation of glycemic levels on intake of the offending drugs. The twice positive dechallenge and a positive rechallenge are suggestive of a causal relationship of the drugs with the event. According to the Naranjo scale for causality assessment, the association of pentoxifylline and cilostazol with hyperglycemia was probable (score of 6) [5]. The WHO – UMC causality assessment qualified the event as possible [6].

The underlying mechanism of hyperglycemia could be due to significantly enhanced expression of GLUT2 on jejunal enterocytes, thus leading to the highest rate of intestinal glucose absorption in presence of pentoxifylline [7]. While some of the absorbed glucose is used for cellular metabolism, the remaining crosses the basolateral membrane into circulation via GLUT2 [7]. Another mechanism contributory to the effect could be the activation of high-affinity, low capacity transporter SGLT-1, also involved in intestinal glucose absorption, by cAMP. This is supported with the finding that both pentoxifylline and cilostazol increase cAMP by inhibition of phosphodiesterases. Our hypothesis is that phosphodiesterase inhibitors i.e. pentoxifylline and cilostazol could favour intestinal glucose absorption through a direct pathway involving increased cAMP levels and another mechanism requiring enhanced GLUT2 expression [7]. Hence, we propose a combined effect of pentoxifylline and cilostazol causing drug induced hyperglycemia in this patient.

**CONCLUSION**

Thus the case study of this patient has revealed that the phosphodiesterase inhibitors, pentoxifylline and cilostazol could be causally related to the hyperglycemic event. Although, the precise mechanism is unclear, we hypothesize that increased intestinal glucose absorption leading to altered glucose homeostasis could have precipitated the adverse event. Therefore it is strongly recommended that monitoring the glycemic levels of all the patients being prescribed pentoxifylline and cilostazol is imperative, especially if the patient is also a diabetic.

**ACKNOWLEDGEMENTS**

We take this great opportunity to thank PSG hospitals and its sister institutions to providing necessary facilities and continuous support in all our activities.

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Auramine-o and Malachite Green Poisoning: Rare and Fatal

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ABSTRACT

Traditionally, it was believed that the cow dung has germicide property. In modern era, due to unavailability of actual cow dung, people started using commercially available synthetic one. The synthetic cow dung powder called 'Sani Powder' in local parlance used to clean courtyards, house and temple premises. It is a dye which can be a lethal poison with no available antidote. Cow dung powder is available in two different colors: yellow powder (Auramine-O) and green powder (Malachite Green), commonly used in rural Tamil Nadu (South India) in the districts of Coimbatore, Tirupur and Erode. Even though the sale is legally banned, the powder is easily available in grocery shops. The high toxicity profile of the dye is evident from limited toxicological data demonstrated from clinical and experimental studies. Auramine is a life-threatening neurotoxic and also causes severe hepatic damage. Animal and observational research confirms that Malachite Green is a multi-organ toxin with delayed toxicity. Very few cases have been reported with Auramine poisoning while there are no references so far about Malachite Green poisoning.

Keywords: Auramine poisoning, Dye, Hepatotoxicity, Malachite Green, Neurotoxicity.

INTRODUCTION

Ancient history of south-Indian culture regarding their personal hygiene and community welfare etc is mentioned in many places in the literature. During that period, people cleaned the living premises using cow dung but now people use commercially available powder which is synthetic and in local parlance known as 'Sani Powder' and is commonly used in South-India (Tamil Nadu) to clean courtyards, house and temple premises. It is used as a germicide but the chemical being used is a dye. It is basically composed of Auramine-O (diaryl methane dye) as yellow powder and Malachite Green (triphenyl methane dye) as green powder. Though the sale is legally banned, the powder can be cheaply purchased from grocery shops at Rs.5 per packet. In rural Tamil Nadu (South India), especially in the districts of Coimbatore, Tirupur and Erode cow dung powder is commonly used as a suicidal poison. There is no specific antidote for these dyes. It has a very high toxicity profile due to which death occurs within hours of ingestion. Auramine is a neurotoxic poison which causes CNS depression which is clearly manifested from the low Glasgow Coma Scale (GCS). Severe hepatic damage as a result of centrilobular necrosis due to toxic metabolite related toxicity may be illustrated by jaundice, upper abdominal pain, and vomiting. Auramine being a cationic dye causes severe ocular injury on eye contact and damages the gastrointestinal mucosa on ingestion. Chronic effects of Auramine dye include carcinogenicity, mutagenicity and its long term inhalation leads to pneumoconiosis. Malachite Green is a multi-organ toxin which shows delayed toxicity. Rarely do these cases get referred to tertiary or teaching hospitals which add to the reason why synthetic cow dung poisoning is not reported in literatures.¹

CASE REPORT 1

A 19 year old male ingested yellow sani powder with the intention of committing suicide. He was taken to a nearby government hospital with complaints of yellow discoloration of oral cavity, epigastric pain and abdominal discomfort. Gastric lavage was given and he was referred to a higher center. He was brought to the hospital after an hour. On examination he was conscious, tachycardic with a pulse rate of 140beats/min, blood pressure 110/80mmHg, respiratory rate was 40 breaths/min, SpO₂ 89%, GCS was 10/15 (E4 V2 M4) and he was icteric. Ultrasound (USG) abdomen revealed mild hepatomegaly, had no transaminitis and the patient was hyperglycemic. ABG analysis showed metabolic acidosis with hypoxia. He was closely monitored and supportively managed in ICU for two days. On the fourth day he had acute hepatitis with SGPT of 140beats/min, blood pressure 110/80mmHg, respiratory rate was 40 breaths/min, SpO₂ 89%, GCS was 10/15 (E4 V2 M4) and he was icteric. Ultrasound (USG) abdomen revealed mild hepatomegaly, had no transaminitis and the patient was hyperglycemic. ABG analysis showed metabolic acidosis with hypoxia. He was closely monitored and supportively managed in ICU for two days. On the fourth day he had acute hepatitis with SGPT of 693U/L (normal upto 37U/L) and total billirubin of 4.36mg/dL (normal upto 1mg/dL). His coagulation parameters were also prolonged with Prothrombin time 21 seconds (control 14 seconds) and INR 1.72. He was treated with intravenous injection of Vitamin K. Progressively on the sixth day patient had vomiting and severe transaminitis with SGPT of 2050U/L. On further treatment, the SGPT decreased to 895U/L and total bilirubin decreased to 1.08mg/dL as on the ninth day. Patient was stabilized and discharged on the 10th day.
**CASE REPORT 2**

A 31 year old woman consumed unknown quantity of yellow cow dung powder as a suicide attempt. She was rushed to a nearby hospital and gastric lavage was given. She was referred to a tertiary hospital for higher care. On the way, she had developed recurrent episodes of seizure (status epilepticus). She was brought to the hospital unconscious and in gasping state. She also had frothy secretions from her mouth. On examination, her pulse rate was 139 beats/min, blood pressure 140/60mmHg, SpO\textsubscript{2} was 67\% and GCS was 4/15 (E1 V1 M2). She was intubated, revived and shifted to ICU. She was hypoxic with aspiration pneumonitis and ABG analysis showed metabolic acidosis. Her coagulation parameters were prolonged with Prothrombin time 20 seconds (control 14 seconds) and INR 1.65. She was hyperglycemic and had no transaminitis. She responded well to treatment and weaned from ventilator after 16 hours on the second day and shifted to room. On the fourth day, she had severe transaminitis with SGPT of 644U/L and total bilirubin of 6.72mg/dL which gradually reduced later. She was stabilized, slowly recovered and was discharged on the sixth day.

**CASE REPORT 3**

A 28 year old female was brought to our hospital an hour after consumption of green cow dung powder in an attempt to suicide. She had complaints of vomiting within 5 minutes of consumption and burning sensation over the abdomen. On examination, she was conscious, pulse rate 116 beats/min, blood pressure 90/60mmHg, respiratory rate 24 breaths/min, SpO\textsubscript{2} was 98\% and GCS was 15/15. Next day she had cough with expectoration, bilateral wheeze on auscultation and bronchitis. Her cough persisted for four days. She also had episodic chest pain and discomfort. She had no transaminitis. Patient was closely monitored, stabilized with intravenous fluids, antibiotics and bronchodilators, counseled and discharged on eighth day.

**DISCUSSION**

Auramine-O is a yellow dye with a molecular formula of C\textsubscript{35}H\textsubscript{26}N\textsubscript{6}HCl. Toxicological data demonstrated in different animal models show acute oral LD\textsubscript{50} of 150-1500 mg/kg. Other studies also confirm DNA damage induced by Auramine in liver, kidney, and bone marrow of rats and mice, and in human cell line. Eye contact of Auramine (cationic dyes) produces a range of injuries from conjunctival oedema, hyperemia and purulent discharge to total opacification. Chronic health effects after exposure to Auramine are carcinogenic and mutagenic with higher incidence of bladder cancer, lymphatic cancer and also cause reproductive damage in humans.\(^3\) Long term inhalation causes pneumoconiosis which results from sedimentation of particles less than 0.5 micron in the lungs. Surprisingly, there are no cautionary labels on the packet despite being a known poison in the locality. Even though it is legally banned, the poison is widely available in market and no step was taken to prevent it.

Acute exposure initially shows neurological features like convulsions, non-specific muscle cramps, spasms, focal deficit and coma. Except for any primary focal neurological deficit, seizures are one of the deadly events caused by many poisons. The sudden onset of seizure episode in poisoning signifies the involvement of both the cerebral hemispheres. Direct CNS effect of the poison is clearly evident from the low GCS score of the patients. Patients show severe jaundice and late transaminitis due to centrilobular necrosis of liver and biliary stasis. Centrilobular necrosis is often dose-related or toxic metabolite related hepatotoxicity. The damage spreads outward from the middle lobe of the liver. Mild necrosis is due to small amounts of parenchymal damage with asymptomatic transaminitis. Severe necrosis is accompanied either by nausea, vomiting, upper abdominal pain and jaundice.\(^3\) The yellow dye is a GI tract irritant which causes damage to the mucosal membrane hence, causing epigastric pain and discomfort.

The similarity between the two yellow cow dung poisoning were tachycardia over a short duration of time, metabolic acidosis and they both were hyperglycemic. These were not reported in any literatures before.

Malachite Green has a molecular formula of C\textsubscript{35}H\textsubscript{35}N\textsubscript{5}Cl and is traditionally used as dye. It's also used as a parasiticide in fish industry. No human experimental and toxicological studies are available. Chemical safety data demonstrated in animal (mouse) model shows acute oral LD\textsubscript{50} of 80-120 mg/kg.\(^4\) Interestingly rats fed malachite green illustrated a dose related liver damage along with hepatic tumors and lung adenomas.\(^3\) Clinical and experimental observations reported so far revealed that malachite green is a multi-organ toxin and takes a while longer to affect the organs. It is very difficult to state whether the cough with expectoration, bilateral wheeze, chest discomfort and bronchitis in the case report 3 is due to the direct action of the toxin in the respiratory system. Also there is no case report published on Malachite Green toxicity in humans.

**CONCLUSION**

The treatment of poisoning caused by an uncommon compound is a challenge and the situation becomes graver when the patient does not respond properly on treatment. Further studies are necessary to elucidate this rare and fatal poison in a broader aspect and this article will serve as a guide for future research. The authors wish to highlight the easy availability of such fatal poisons must be banned completely.
from the market and necessary action should be taken against those who sell them.

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REFERENCES

Sickle Cell Disease and Superstitions: An Interesting Study Report

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ABSTRACT

This study focuses on four interesting cases of sickle cell anaemia in rural areas of Chhattisgarh (CG) state. CG is a young state of growing central India with highest resources of minerals, iron, herbs and rice cereals. These patients were identified during a sickle cell disease management programme conducted by Faculty of Pharmaceutical sciences, Shri Shankaracharya Group of Institutions, Bhilai, CG. The study reveals all the patients were from poor backward communities. Symptoms related to malnutrition and infections were mostly intermingled with anaemia but all of them were least interested to follow any treatment. They were following some ‘janbuti’ from years which had worsened their conditions. There details history was taken from them and counselled them so that they understand the scope of the problem and participate in the management of the disease.

Keywords: Blood disorder, Chhattisgarh, India, Sickle cell anaemia, patient counselling.

INTRODUCTION

Sickle cell anaemia is of hereditary in nature and is a result of an abnormal type of red blood cells. People with this disorder have atypical haemoglobin molecules called 'hemoglobin S', which can change the shape of normal red blood cells into a sickle, or crescent, shape. When red blood cells sickle, they break down prematurely, which can lead to anaemia. These irregularly shaped cells get stuck in the blood vessels and are unable to transport oxygen effectively, causing pain and damage to the organs. One interesting fact about the disease is unlike normal RBC's sickle-shaped cells live only 10 to 20 days. Sickle Cell trait (Hb AS) is a healthy carrier state which does not give rise to a significant clinical presentation.

In India several states are reporting Sickle cell disease from years. The prevalence of sickle haemoglobin from various parts of Madhya Pradesh and Chhattisgarh varied from 15 to 30 percent. Chhattisgarh is a young state of central India. The majority of the people in this state belong to a non-educational background. Their existence is predominantly with agriculture and often lives in remote areas. They are not blessed with the shower of education. The population which are illiterate believe that this is a curse of god. Poor economic condition is also a rival of them. Previously various other researchers also have reported several data on this disease in different areas of this state.

CASE STUDY

In the course of studies of cases of chronic sickle cell anaemia here we reported details of four cases. They belonged to other backward caste (OBC) and schedule caste (SC) communities. There clinical and haematological data's are presented in table I and II respectively. Following details were obtained from these patients:

Case 1: Mr. C.L. Sahu (caste OBC), student, suffering from this disease for more than 10 years. He belongs to a family of four members in which his mother and sister is a chronic sufferer of this disease. His father is not a patient neither a sickle trait. Mr. Sahu reported about his chronic joint pain, sever weakness and low haemoglobin count. Often he gets various other infections. He often suffers from fever and cold. The fever is malaria positive. Occasionally he undergo with blood transfusion. He is under the treatment of some local herbal medicines.

Case 2: Mrs. P. Sona (caste SC), house wife of 34 years age, suffering from this disease for more than 10 years. She has four girl children but by God's grace no one is a patient of Sickle cell disease (no information about sickle trait). Her husband is not a patient neither a sickle trait. Mrs Sona reported about his chronic joint pain, sever weakness and low haemoglobin count. Often he gets various other infections. He often suffers from fever and cold. The fever is malaria positive. Occasionally he undergo with blood transfusion. He is under the treatment of some local herbal medicines.

Case 3: Ms. I. Sona (caste SC) of 18 years old is a victim of this disease. She is suffering from whole body swelling, extreme low haemoglobin level and severe viral infections. Relapsing fever is a frequent trouble she faces. She was a school going student but the inferior health condition forced her to leave school. Her mother is also a patient of this disease.

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but father is safe. She often got blood transfusion and other emergency treatment. Now she is following ayurvedic treatment but no significant changes in her condition is reported.

**Case 4:** Mrs. B. Sahu (caste OBC), house wife, reported her sickness for more than 10 years. She has severe anaemia along with joint pain and weakness. She never followed any treatment except “jaributi”. She believes this disease is a curse.

**DISCUSSION**

The cases which we discover were belong to Teli and Dom communities. Dom is a social group also called as 'chandala' scattered across India. Its presumed root, ḍom, which is connected with drumming, is linked to damara and damaru. The Dom community is traditionally an occupational caste. Their main occupation is making a variety of baskets and sells them. They are Sudra and known as Achhut (Untouchable). Teli is a caste traditionally occupied in the pressing of oil in India, Nepal and Pakistan. The word Teli comes from Tel, which means oil in Marathi, Hindi, and Oriya languages. All these castes are very backward with their education and believe till date. There community is used to practice endogamy and consanguineous marriages. This is a prime cause of spreading the disease because if one parent has sickle-cell anaemia (SS) and the other has sickle-cell trait then there is a 50% chance of a child's having sickle-cell disease and a 50% chance of a child's having sickle-cell trait. When both parents have sickle-cell trait a child has a 25% chance of sickle-cell disease.

In all these cases there was a history of antecedent anaemia, jaundice, and episodes of bone, joint and abdominal pains characteristic of crises. Their features showed facies with prominent frontal bosses and cheek bones. Fever was a distinctive feature in all these patients. Malaria is endemic in these areas but it was ruled out by repeated peripheral blood examination for the presence of parasites. In the case of sickle cell anaemia it has been postulated that malarial infection precipitates crisis. The previous history of fever, bouts of crises and low haemoglobin count may be due to antecedent malarial infection which was difficult to rule out except at the time of investigation of the patients.

The interesting point was after having all these serious manifestations they were indifferent. They love to believe in jaributi, jharfuk and similar superstitions. They think the disease is spreading due to God's revenge. Even after getting counselling about the disease management programme two of them (Mrs. B. Sahu and Mrs. P. Sona) were less interested about pre-marriage blood test and pre-natal diagnosis. But the young group was rational and they were encouraged by this management programme.

**CONCLUSION**

It must be emphasized that reports of sickle cell anaemia in India are rare and in Chhattisgarh is few. This is because here has been a lack of awareness of the disease entity in these regions, together with the difficulty in making a rapid and certain diagnosis. Mass awareness programme and patient counselling are needed to manage the disease in micro level. The infra-structural facilities and technical knowhow for diagnosis of the disorder and its clinical management should be generated at district hospital level depending upon the disease load.

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