Regulatory Pertaining To Herbal Drugs and Dietary/Herbal Supplements In India: Concern For Safety

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ABSTRACT

Herbal drugs constitute a major share of all the officially recognized system of medicine in India Viz. Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy. More than 70% of India's population resort to such traditional medical practices and currently, not less than 80% of people worldwide use herbal medicinal products and supplements. Although therapies involving these agents have shown promising potential with the efficacy of a good number of herbal products clearly established, many of them remain untested and their use are either poorly monitored or not even monitored at all. The consequence of this is an inadequate knowledge of their mode of action, potential adverse effects and interactions with allopathic medicines to promote both safe and rational use of these agents. Since, safety continues to be a major issue with the use of herbal remedies, it becomes imperative, therefore, that relevant regulatory authorities put in place appropriate measures to protect public health by ensuring that all herbal medicines are safe and of suitable quality. Several regulatory guidelines are currently available in India for herbal drugs including those for traditional medicines, over-the-counter hebalsvand dietary supplements. Harmonization and improvement in the processes of regulation is therefore needed.

Key words: Herbal medicine, Herbal/dietary supplements, Regulatory aspects, Conventional medicine, Allopathy, Alternative systems of medicine.

INTRODUCTION

India, the sacred land of herbal medicine has a very long, safe and continuous usage of many herbal drugs in the officially recognized alternative systems of medicine viz. Ayurveda, Yoga, Unani, Siddha, Homeopathy and Naturopathy. Millions of Indians use herbal drugs regularly as spices, home remedies, health foods, over the counter (OTC) as self-medication or as drugs prescribed in the non – allopathic systems1. The use of herbal medicines and phytonutrients or nutraceuticals is expanding rapidly across the world for treatment of various health challenges in different national healthcare settings2. In the past decade there is a tremendous surge in acceptance and public interest in natural therapies both in developing and developed countries. Thereby the availability of herbal medicines has reached a stage from drug stores to food stores and super markets3.

The important reasons of seeking herbal therapy is the belief that they are safe, no adverse effects, promotes healthier living and can be used along with conventional medicine (allopathy). Herbal medicines are therefore often viewed as a balanced and moderate approach to disease treatment and individuals use them as home remedies and OTC drugs, spend huge amount of money on herbal products4. This has contributed to an increase in international trade in herbal medicine enormously and has attracted most of the pharmaceutical companies, including the multinationals. The current turnover of herbal drug industry is approximately 15000 crore5.

As the global use of herbal medicinal products continues to grow and many more new products are introduced into the market, public health issues and concern surrounding their safety are also increased. Although many herbs have a long history of use and of claimed health benefits their potent pharmacologic

activity may contribute to potential adverse effects and drug interactions6. It is also common knowledge that the safety of most herbal products is further compromised by lack of suitable quality controls, inadequate labelling and absence of appropriate patient information7. Discussion in this review is limited to the regulatory aspects of herbal medicines in India.

Factors responsible for the increased use of herbal medicine by the public/growth of herbal medicine market:

The recent resurgence of public interest in herbal remedies is attributed to several factors some of which include: affordability, closely relates to the patient ideology, reduces concerns about the adverse effects of synthetic medicines, health promotion and safe therapy of chronic, life threatening conditions, especially since conventional medicine is ineffective in the treatment of diseases, such as advanced stages of cancer and of new infectious diseases. Furthermore, traditional medicines are widely perceived as being natural, safe and hence non toxic. On the contrary there are reports pointing to adverse events associated with herbal drug usage especially when taken along with prescription drugs, over-the-counter medications or other herbs3,4,8,9.

Concerns about the safety of herbal medicine:

The major problem associated with the use of herbal medicine arises mainly from the classification of many of the herbal medicine as foods or dietary supplements in many countries. Evidence of quality, efficacy and safety of these herbal medicines are not being required before marketing, the quality tests and production standards tend to be less rigorous or controlled. The safety of such herbal medicines has therefore become a major concern to both national health authorities and the general public.

The legal process of regulations and legislation of herbal medicines changes from country to country. The reason for this involves mainly cultural aspects and also the fact that herbal medicines are rarely studied scientifically. The WHO has published in order to define basic criteria for evaluating the quality, safety and efficacy of herbal medicines aimed at assisting national regulatory authorities, scientific organizations and manufacturers in this particular area10.

Regulations pertaining to herbal medicine in India:

To ensure and enhance the quality of herbal medicines, the Government of India has notified Good Manufacturing Practices (GMP) under Schedule 'T' of the Drugs and Cosmetics Act 1940 which also ensures that the raw materials used in the manufacture are authentic, of prescribed quality and are free from contamination. The guidelines for Good Agricultural Practices (GAP) seek to lay down a cultivation programme designed to ensure optimal yield in terms of both quality and quantity of any crop intended for health purposes. Quality of raw material being watched over by following GAP and GACP, for manufacturing the prepared drugs, government has formulated the Drugs and Cosmetics act 1940. It is an act to regulate the import, manufacture, distribution and sale of drugs and cosmetics. This act was basically initiated for chemical drugs but later in the year 1969 a separate chapter relating to Ayurveda, Siddha and Unani drugs was inserted by act 13 of 1964. Later this as again modified with some substitution in the year 1983, 1987, 1994 and 200211,12. The schedules and rules pertaining to Ayurveda, siddha and Unani systems in the act are:

Schedules:

- First Schedule substituted by act 13 of 1964 came into force w.e.f 1-2-1969. The schedule lists the standard Indian Pharmacopoeias to be followed for manufacturing Ayurveda, Siddha and Unani drugs. About 57 books of Ayurveda (with insertions in 1987, 1994, 2002), 29 of Siddha (1987), 13 of Unani Tibb system are listed.
- Second Schedule came into force w.e.f 15-09-64. It states about the standard to be complied for manufacturing drugs. (Subs. by Notifn. No. G.S.R. 885, dated the 4th August, 1973, Gazette of India, Pt. II, s. 3(i), p. 1643.)
- SCHEDULE-E(1) : List of poisonous substances under the Ayurvedic (including Siddha) and Unani Systems of Medicine (Added by Notfn. No. 123/67D dt. 2-2-1970) differentiated into vegetable, animal and mineral origin.
- SCHEDULE T: Good Manufacturing Practices (GMP) for ayurvedic, siddha and unani medicines. (Ins by G.S.R. 561 (E) dt 23-06-2000 and subs. by

G.S.R. 198(E), dt. 7.3.2003.). Under Schedule "T" of the drugs and cosmetics act 1940, the government has made it mandatory for all manufacturing units to adhere to GMP.

Rules:

- Rules: Part XVI (Parts XVI, XVII and XVII added by S.O. 642, dt. the 2-2-1970 (w.e.f. 21.2.1970) Manufacture for sale of ayurvedic (including siddha) or unani drugs. It notifies about how to acquire license, loan for establishing a unit and also on the identification of raw materials and its purity.
- Part XVIA: Approval of institutions for carrying out tests on ayurvedic, siddha and unani drugs and raw materials used in their manufacture on behalf of licensees for manufacture for sale of ayurvedic, siddha and unani drugs (Ins. by G.S.R. 701(E), dt. 27-7-2001 and subs. by G.S.R.73 (E), dt. 31-01-2003.)
- Part XVII: Labelling, packing and limit of alcohol in ayurvedic (including siddha) or unani drugs. (Subs. by G.S.R. 904(E), dt. 2.11.1992.)
- PART XVIII: Government analysts and inspectors for ayurvedic (including siddha) or unani drugs.
- PART XIX: Standards of ayurvedic, siddha and unani drugs (Ins. by G.S.R. 519(E), dt. 26.6.1995.)

Regulations pertaining to Herbal supplements/Dietary supplements/Nutraceuticals in India:

The term 'Nutraceutical' as per Food Safety and Security Act, India (passed in 2006, yet to be implemented) includes a list of ingredients a nutraceutical product could have as well as its general properties. As per this Act a traditional medicine cannot be classed as a nutraceutical. Foods for special dietary use are specifically processed or formulated to satisfy particular dietary requirements which exist because of a physical or physiological condition or specific disease and disorder. These are presented as such, where in the compositions of these foodstuffs must differ significantly from the Indian Standard (IS) composition of ordinary foods of comparable nature, if such ordinary food exists and may contain one or more of the following ingredients, namely:

- Plants or botanicals or their parts in the form of powder, concentrate or extract in water, ethyl alcohol or hydro alcoholic extract, single or combination.
- Minerals or vitamins or proteins or metals or their compounds or amino acids (in amounts not exceeding the Recommended Daily Allowance (RDA) for Indians) or enzymes with permissible limits
- Substances of animal origin
- Dietary substances for use by human beings to supplement the diet by increasing the total dietary intake13.

Food Safety and Standards (FSS) Act was passed by the parliament in 2006. In 2008, Food Safety and Standard Authority of India (FSSAI) came into existence.

1. The FSSAI will make rules and frame standards to regulate nutraceuticals as outlined in the Food Safety Act, 2006.
2. Food Safety and Standard Act 2006 consists of 12 chapters and chapter IV article 22 of the Act addresses nutraceutical, functional food, dietary supplements and need to regulate these products such that anyone can manufacture, sell or distribute or import these products. These products include novel foods, genetically modified article of food, irradiated food, organic food, and food for special dietary uses, functional food, nutraceuticals and health supplements.
3. Article 23 and 24 address the packaging and labelling of food and restriction of advertisement regarding foods.
4. A product that is labelled as "food for special dietary uses" functional food or nutraceutical dietary supplements which is not represented for use as conventional food and whereby such products may be formulated in the form of powders, granules, tablets, capsules, liquids, jelly and other dosage forms but not parentrals, and are meant for oral administration.
5. Nutraceutical products do not claim to cure or mitigate any specific disease, disorder or condition

(except for certain health benefit or such promotion claims) as may be permitted by the regulations made under this Act.

6. It does not include a narcotic drug or a psychotropic substance as defined in the Schedule of the Narcotic Drugs and Psychotropic Substances Act, 1985 and rules made there under and substances listed in Schedules E and EI of the Drugs and Cosmetics Rules, 1945;

7. It also includes "genetically engineered or modified food which means food and food ingredients composed of or containing genetically modified or engineered organisms obtained through modern biotechnology, or food and food ingredients produced from but not containing genetically modified or engineered organisms obtained through modern biotechnology; "organic food" means food products that have been produced in accordance with specified organic production standards; "proprietary and novel food" means an article of food for which standards have not been specified but is not unsafe.

8. With the draft guidelines, there may be provisions of testing and tracing the origin of the food products right back up to farm level.

9. The Authority would also have to grapple with the gigantic task of putting in place the minimum levels of compliance of food laws, administrative efficiency, transparency and an independent audit system.

10. Under the new rule each state will have a food safety commissioner who would be the implementing agency.

CONCLUSION:

The global acceptance and use of herbal medicines and related products continue to assume exponential proportions. Therefore, regulatory policies on herbal medicines need to be standardized and strengthened on a global scale. Relevant regulatory authorities in different countries of the world need to be proactive and continue to put in place appropriate measures to protect public health by ensuring that all herbal medicines are safe and efficacious.

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Comparative Study on Efficacy and Cost Effectiveness of Equivalent Doses of HMG COA Reductase Inhibitors

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ABSTRACT

Objective: The present study aimed to determine the efficacy and cost-effectiveness of equivalent doses of statins.

Methods: A prospective study was done for 6 months at a multispecialty hospital. The study had a parallel design with the patients randomly assigned into two groups, according to the dyslipidemic agents (atorvastatin/ rosuvastatin) based on inclusion and exclusion criteria. The effects of different doses of rosuvastatin and atorvastain on TC, HDL-C, LDL-C and TG for the two groups were documented from the baseline visit, visit-1 and visit-2. The incremental cost effectiveness ratio (ICER) was determined for the intervention drugs with respect to lipid parameters to estimate the cost per additional unit effect for the most commonly used dyslipidemic drugs which assist in the rational selection of agents in a cost-effective manner.

Results: A significant reduction in TC, LDL-C, TG and a significant increase in HDL-C was observed for rosuvastatin than equivalent doses of atorvastatin .The weighted mean reduction in LDL-C obtained from the results showed that more patients in rosuvastatin group (78%) reached NCEP ATP III LDL C goals than atorvastatin group (68%). While comparing the Average costs of equivalent doses for all the four doses of statins, cost of rosuvastatin was relatively more than Atorvastatin.

Conclusion: The study concluded that rosuvastatin provides better value for money than atorvastatin in lowering lipid levels in clinical practice and to be the most cost-effective treatment regimen for dyslipidemia. This study reports found the fact that the most cost - effective treatment regimen was Rosuvastatin for patients with dyslipidemia.

Key words: Cost Effective analysis, HMG-CoA reductase inhibitors, ICER, Statins.

INTRODUCTION

Dyslipidemia is a broad term that refers to a number of lipid disorders of lipoprotein metabolism including lipoprotein overproduction or deficiency. The basic categories of dyslipidemia include: elevated low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C), excess lipoprotein (a), hypertriglyceridemia, atherogenic dyslipidemia, and mixed lipid disorders. Dyslipidemia, particularly hypercholesterolemia and atherogenic dyslipidemia have been closely implicated in the pathogenesis of coronary heart disease (CHD). Dyslipidemia is a major risk factor for coronary heart disease, the leading cause of death in the United States. Investigations from several groups, have shown that Asian Indians are predisposed to develop type 2 diabetes, proatherogenic metabolic abnormalities (metabolic syndrome, insulin resistance syndrome) and CHD. The metabolic syndrome is a constellation of risk factors such as abdominal obesity, insulin resistance, glucose intolerance, hypertriglyceridemia, low levels of HDL-cholesterol and elevated blood pressure occurring in the same individual. 'Atherogenic dyslipidemia' is associated with metabolic syndrome and may be responsible for accelerated atherosclerosis. Treatment of dyslipidemia can reduce the risk of heart disease by 30% over a 5-year period. Although the benefits of lipid-lowering therapy have been demonstrated most

conclusively in persons with cardiovascular disease, lipid-lowering therapy is effective even in persons without clinically apparent cardiovascular disease. The National Cholesterol Education Program's series of Adult Treatment Panel (ATP) reports have been developed to provide healthcare professionals with recommendations pertinent to detecting and managing dyslipidemia. The efficacy and safety of satins were already well established and this study adds on the cost effectiveness analysis that takes into account relative efficacy and relative pricing amongst different products. Statin drugs are expensive, especially considering the large number of persons who could potentially benefit from cholesterol-lowering therapies. As a result, many analysts have focused on the costs, resource use, and cost-effectiveness of using statins to lower cholesterol levels5. Economic evaluation helps us to prioritize services rationally by providing a scientific, value free frame work. Clinical pharmacist intervention can help in Clinical decision making, Endorsing drug policies, Aid of formulary decision making, Minimization of healthcare cost of the patients, improving patient adherence to therapy and also have an Impact on hospital pharmacy budget.

MATERIALS AND METHODS:

A prospective interventional study was conducted at a 900 bedded tertiary care teaching hospital located in the south region of Tamilnadu. The study was carried out for a period of six months in the Inpatients of Cardiology & General medicine departments and the Drug Information Centre which is a part of the department of pharmacy practice. Male or Female patients of age between 20-65 years who were diagnosed as dyslipidemia at least one year earlier with co-morbid conditions like hypertension, diabetes and cardiovascular disease on dyslipidemic drugs prescribed such as atorvastatin or rosuvastatin as monotherapy and willing to repeat lipid profile were included in the study. Male or female dyslipidemic patients below the age of 20 and above the age of 65 years, with life style modification alone, with dyslipidemic drugs other than atorvastatin and rosuvastatin, patients with co-morbid conditions like psychosis, pregnancy & lactation, critically ill and who were not willing to repeat lipid profile were excluded from the study. The study was commenced after getting the approval from (IHEC) on the month of August 2011 Patients who were diagnosed as dyslipidemia were randomly after obtaining printed informed consent in the colloquial language (Tamil). The study had a parallel design with the Patients randomly assigned into two groups, according to the dyslipidemic agents (atorvastatin/ rosuvastatin) they were taking with hundred patients in each group respectively. Dyslipidemic patients were distributed according to NCEP ATP III guideline and major risk factors. The Risk factor assessment emphasizing cardiovascular health was determined by categorizing into desirable, border line & undesirable for both atorvastain and rosuvastatin groups on their first visit, second visit and final visit. First visit was done after a period of 2 months interval from the baseline visit and second visit after a period of 2months interval from the first visit over a period of six months.

The different brands of dyslipidemic agents like Aztor, Tonact, Rolip &Rosuvas, were documented. The effects of different doses of rosuvastatin and atorvastain on TC, HDL-C, LDL-C and TG for the two groups were documented. The mean percentage reduction in TC, LDL-C, TG and mean percentage increase in HDL-C were statistically analyzed for both the groups. The pharmacoeconomic analysis was conducted using Whole Sale Acquisition Cost (WAC). The WAC is the list price for wholesalers, distributors and other direct accounts before any rebates, discounts, allowances or other price concessions that might be offered by the supplier of the product. Acquisition costs are used for determining comparative costs Efficacy in terms of milligram-equivalent doses and point estimates in mean change in TC, LDL-C, TG, HDL-C and cost per 1% change in lipid values were calculated for determining the cost-effectiveness by dividing the mean average cost (Rs) of the drug by mean efficacy (mg/dl). The actual average drug costs per day was calculated by determining costs for the percentage of patients receiving daily dosage of the prescribed drug and summing the costs in a procedure known as dose stratification. The percentage of patients receiving each dose (the distribution of the doses) is multiplied by the cost of that medication dose to produce the cost per day. The sum of the multiplication products determines the true average cost per day The comparative cost-effectiveness of equivalent doses of HMG-CoA reductase inhibitors

in achieving a predetermined therapeutic goal was estimated and compared in terms of cost, proportions of patient attaining LDL-C goal and mean cost per patient reaching LDL-C goal. The incremental cost effectiveness ratio (ICER) was determined for the intervention drugs with respect to lipid parameters to estimate the cost per additional unit effect for the most commonly used dyslipidemic drugs which assist in the rational selection of agents in a cost-effective manner. The outcome measure was calculated by using the formula and the result was according to ICER quadrant plane.

DISCUSSION

Dyslipidemic patients in the two groups were distributed into desirable, border line and undesirable according to National Cholesterol Education Program Adult Treatment Panel III cholesterol goal. A large number of patients reached the desirable level in the final visit from undesirable and border line condition. While comparing the two groups, more patients in rosuvastatin group reached ATP111 goal than atorvastatin group. This shows that rosuvastatin was more effective than atorvastatin in reducing TC, LDL-C, TG and increasing HDL-C. The results of this study were similar to other studies where statin therapy has been shown to reduce LDL-C, TG and modestly increase HDL-C as shown in Table-1&2.

Comparative efficacy of equivalent doses of rosuvastatin and atorvastatin for a period of six months was studied by comparing the change in the lipid values between the different visits. A significant reduction in TC, LDL-C, TG and a significant increase in HDL-C was observed for rosuvastatin than equivalent doses of atorvastatin which shows that rosuvastatin is more effective than atorvastatin.

Comparative cost of equivalent doses of rosuvastatin and atorvastatin was calculated for six months by using Average drug cost. The average drug cost per day was calculated by multiplying the percentage of patients taking each dose of the drug with the cost of that drug and adding the products together. While comparing the Average costs of equivalent doses for all the four doses of statins, cost of rosuvastatin was relatively more than Atorvastatin. The comparative Cost-effectiveness of equivalent doses of atorvastatin and rosuvastatin for TC, LDL-C, TG and HDL-C was assessed in terms of mean cost per 1% change in lipids per unit of clinical efficacy. A drug which has lowest value for these lipid parameters was taken as cost effective drug. From the above results, with respect to efficacy and the average cost per 1% change in lipid parameters in elevating HDL-C and reducing TC, TG and LDL-C the most cost-effective treatment was rosuvastatin as shown in Table-3&4.

RESULTS

Table - 1: Distribution of patients according to NCEP ATP- 111 guidelines - atorvastatin group

NCEP Classification	TC(n=100)		HDL-C (n=100)		LDL-C (n=100)		TG(n=100)	
	Before	After	Before	After	Before	After	Before	After
Desirable	04	50	00	32	00	56	10	31
Borderline	78	36	50	66	82	30	84	60
Undesirable	18	14	50	02	18	04	06	09

Table - 2: Distribution of patients according to NCEP ATP- 111 guidelines - rosuvastatin group

NCEP Classification	TC(n=100)		HDL-C (n=100)		LDL-C (n=100)		TG(n=100)	
	Before	After	Before	After	Before	After	Before	After
Desirable	00	52	00	44	00	78	10	60
Borderline	58	48	34	56	88	22	90	40
Undesirable	42	00	66	00	12	00	00	00

Table - 3: Comparative cost-effectiveness of equivalent doses of statins in achieving a predetermined therapeutic goal

Drugs	Dose	Average Cost (Rs)	Cost for 6 Months (Rs)	Proportion of Patients Reaching LDL –C goal	Mean cost per Patient Reaching LDL-C goal (Rs)
Atorvastatin	5mg	0.90	166.45	0.42	396.30
	10mg	2.02	371.12	0.53	700.22
	20mg	3.49	638.67	0.59	1,082.49
	40mg	4.53	830.50	0.69	1,203.62
Rosuvastatin	5mg	1.22	223.26	0.58	384.93
	10mg	2.89	528.87	0.78	678.03
	20mg	4.99	913.17	0.84	1,087.10
	40mg	10.94	2002.2	0.90	2,224.66

Table - 4: ICER determination for equivalent doses of statins atorvastatin 5mg vs rosuvastatin 5 mg

Incremental cost	Lipid parameters	Incremental Effect	ICER	Quadrant	Type	Result
56.81 Rs	TC	12.31 mg/dl	4.61	1	high cost and high effect	cost effective
	LDL-C	18.33 mg/dl	3.10	1		
	TG	15.17 mg/dl	3.74	1		
	HDL-C	10.14 mg/dl	5.60	1		

The improved efficacy resulted in significantly more patient's achieving the recommended LDL-C goal with rosuvastatin than atorvastatin. The weighted mean reduction in LDL-C obtained from the results showed that patients in rosuvastatin group (78%) and atorvastatin group (68%) reached NCEP ATP 111 LDL cholesterol goals. The mean cost per patient reaching LDL-C goal for rosuvastatin was (Rs 1,175.49) and for atorvastatin (Rs 864.98). It is essential to compare not only the cost of the drug, but also the clinical effect produced by that drug, cheaper does not necessarily mean better value. This shows that cost-effectiveness of rosuvastatin was high than that of atorvastatin in achieving a predetermined therapeutic goal as shown in table-5

Table - 5: ICER determination for equivalent doses of statins atorvastatin 10 mg Vs rosuvastain 10 mg

Incremental cost	Lipid Parameters	Incremental Effect	ICER	Quadrant	Type	Result
157.75(RS)	TC	15.95 mg/dl	9.89	1	high cost and high effect	cost effective
	LDL-C	19.11 mg/dl	8.25	1		
	TG	17.02 mg/dl	9.27	1		
	HDL-C	7.02 mg/dl	22.47	1		

Table - 6: ICER determination for equivalent doses of statins atorvastatin 20 mg and rosuvastain 20 mg

Incremental cost	Lipid Parameters	Incremental Effect	ICER	Quadrant	Type	Result
274.50(RS)	TC	14.28 mg/dl	19.22	1	high cost and high effect	cost effective
	LDL-C	26.36 mg/dl	10.41	1		
	TG	18.88 mg/dl	14.54	1		
	HDL-C	14.69 mg/dl	18.69	1		

Table - 7: Incremental cost-effectiveness ratio (ICER) for equivalent doses of statins atorvastatin 40 mg Vs rosuvastatin 40 mg

Incremental cost	Lipid Parameters	Incremental Effect	ICER	Quadrant	Type	Result
1,171.70	TC	22.78 mg/dl	51.44	1	high cost and high effect	cost effective
	LDL-C	31.08 mg/dl	37.69	1		
	TG	35.94 mg/dl	32.60	1		
	HDL-C	33.40 mg/dl	35.07	1		

Cost- effectiveness was assessed for equivalent doses of statins by means of ICER decision matrix and quadrant plane for all the lipid parameters, the statin which has lowest ICER was taken as cost effective drug. According to ICER determination all the four equivalent doses of rosuvastatin were most cost effective than equivalent doses of atorvastatin for different lipid parameters. Among the four different doses of rosuvastatin, the most cost effective treatment regimen for lowering TC was rosuvastatin 5mg and10 mg. The most cost-effective treatment regimen for increasing HDL-C was rosuvastatin 40 mg, 10mg and5mg. The most cost effective treatment for decreasing LDL-C was rosuvastatin 20 mg, 10mg and 5mg. The most cost-effective treatment regimen for decreasing triglycerides was rosuvastatin 20 mg, 10 mg and 5mg.

CONCLUSION

The analysis complimented the subject of the study. These results confirmed the impact of clinical pharmacist interventions in pharmaceutical care with an emphasis for including consultation with pharmacist relevant in health care system. This analysis employed objective comparative efficacy data obtained from peer-reviewed sources to compare the economic and clinical outcomes of rosuvastatin and atorvastatin in the treatment of hypercholesterolemia. The acquisition cost of rosuvastatin was higher than an equivalent milligram dose of atorvastatin, depending on the dosage used. However, because of the greater milligram potency of rosuvastatin, it is a more cost-effective alternative. Rosuvastatin therefore provides better value for money than atorvastatin in lowering lipid levels in clinical practice. According to the ICER Quadrant plane and Decision matrix, all the four doses of rosuvastatins had high cost and more effect and they lie in the first quadrant. So it establishes the fact to be the most cost-effective treatment regimen for dyslipidemia.

This study had gained a great deal to understand the socio-economic order of patients and a tremendous insight to problems faced by people across the spectrum where the role of the pharmacist was responsible., also supports the idea that well-designed formularies should consider cost-effective drug based on safety,

effectiveness, and cost. Clinical pharmacist play an important role in cost analysis because it benefit not only the patient but also health care system. This study concludes to establish that integration of the pharmacy benefit management with other medical management was highly essential in providing the best human care.

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Formulation and Evaluation of Aceclofenac Fast Dissolving Tablets Using Crospovidone and Crosscarmellose Sodium as Superdisintegrants

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ABSTRACT

Fast dissolving tablets (FDTs) are solid dosage forms that disintegrate and dissolve in the mouth either on or beneath the tongue or in the buccal cavity without water. In this study, an attempt was taken to enhance the solubility and dissolution character of Aceclofenac, a poorly water soluble non steroidal anti-inflammatory drug, by preparing FDTs of Aceclofenac using crospovidone and crosscarmellose sodium as superdisintegrants by direct compression method. The interaction between drug and superdisintegrant was characterized by IR spectroscopic studies. The final blend of the drug and excipients were evaluated for various precompression parameters like angle of repose, bulk density, tapped density, compressibility index, hausner's ratio and post compression parameters like thickness, hardness, weight variation, friability, disintegration time, drug content, wetting time, water absorption ratio and in vitro drug release study. The IR results showed no interactions between the drug and superdisintegrant used. The wetting time was considerably reduced in tablets containing crospovidone which may be due to wicking effect of crospovidone. Among all formulations, formulation F1 showed more water absorption ratio due to its more swelling capacity. Formulation F1 prepared by using crospovidone showed a better percentage of drug release when compared to F2 prepared by crosscarmellose sodium as superdisintegrant. The results revealed that the formulation F1 containing crospovidone (5%w/w) as superdisintegrant provided a faster drug release compared with F2 prepared by crosscarmellose sodium as superdisintegrant.

Key words: *Aceclofenac, Crospovidone, Crosscarmellose sodium, Direct compression, Fast dissolving tablets, Superdisintegrant.*

INTRODUCTION

Many patients express difficulty in swallowing tablets and hard gelatin capsules, tending to non-compliance and ineffective therapy. Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is fast dissolving tablets1. Fast dissolving tablets are solid dosage forms containing medicinal substances which disintegrate / dissolve rapidly in oral cavity within 15-60 sec without water2. The bioavailability of FDTs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drug thereby the amount of drug that is subjected to first pass metabolism is reduced.

Aceclofenac is a new generation Non-Steroidal Anti-Inflammatory drug used in the symptomatic treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis3.Aceclofenac is practically insoluble in water.

Because of its poor aqueous solubility, conventional Aceclofenac dosage forms shows absorption problem and its dissolution is considered to be rate determining step in its absorption from gastro- intestinal tract. The present work was aimed to increase the rate of dissolution of Aceclofenac, thus providing faster rate of absorption by adding crospovidone and crosscarmellose sodium as superdisintegrants in 5%w/w concentration. Mannitol and saccharin sodium were used as sweetening agents to mask the bitter taste of Aceclofenac.

MATERIALS AND METHODS:

Materials:

Aceclofenac was procured from Microlabs Pharmaceuticals, Hosur, India. Microcrystalline cellulose and mannitol were procured from S.d fine- chem., Pvt. Ltd, Mumbai, India. Crosscarmellose sodium was procured from Spectrum Chemicals & Laboratories Pvt. Ltd., Mumbai. Crospovidone, saccharin sodium and talc were procured from Loba Chemie., Pvt. Ltd, Mumbai, India. All other reagents used were of analytical grade.

Methods:

Preparation of Aceclofenac FDTs:

Fast dissolving tablets of Aceclofenac was prepared using crospovidone and crosscarmellose sodium as superdisintegrants in (5% w/w) concentration by direct compression method. All the ingredients were passed through mesh No: 60 separately and collected4. The drug, mannitol, microcrystalline cellulose and crospovidone were mixed uniformly with gentle trituration using mortar and pestle to get a uniform mixture. Finally saccharin sodium and talc were added and mixed well.

The powder blend was then compressed using 7mm punch on 10 stations "B" Tooling Rotatory Tablet punching machine to produce flat- faced tablet, weighing 200mg each at 4kg/cm2 force. The same procedure was followed to prepare tablets of Aceclofenac with crosscarmellose sodium as superdisintegrant and without superdisintegrant (Control-F3). Before tablet preparation, the powder blend of all the formulations were subjected to compatibility studies (IR) and Precompression parameters like Angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The composition of Aceclofenac tablet formulations were shown in Table 1.

Table No.1 Composition of Aceclofenac Fast Dissolving Tablets

S. No	Ingredients (mg)	Formulation Code		
		F1	F2	F3
1	Aceclofenac	100	100	100
2	Crospovidone	10	_	-
3	Crosscarmellose sodium	-	10	-
4	Mannitol	20	20	20
5	Microcrystalline cellulose	61	61	71
6	Saccharin sodium	5	5	5
7	Talc	4	4	4
Weight of each tablet = 200 mg				

Pre compression parameters:

The powder blend was evaluated for pre compression parameters like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The angle of repose was determined by funnel method5. Bulk and tapped density were determined using digital bulk density apparatus. The compressibility index of the powder blend was determined by Carr's compressibility index and the Hausner's ratio was calculated by using the formula:

Hausner's Ratio = Tapped density/ Bulk density.

Carr's index (%) = [(TD-BD) / TD] ×100.

Where, BD-Bulk density, TD-Tapped density

IR Spectral Analysis:

It was used to study the interactions between the drug and the excipients6. The KBR disk method was used for preparation of sample and spectra were recorded over the wave number 3500 to 500 cm-1 in a SHIMADZU FT-IR (model- 8400) spectrophotometer. IR spectral studies of Pure Aceclofenac and Aceclofenac containing highest proportion of individual superdisintegrant were carried out. If there was no change in peaks of mixture when compared to pure drug, it indicates the absence of interactions.

Post compression parameters:

Thickness:

Thickness of tablets was determined using Vernier caliper7. Five tablets were used for the test and average values were determined. The thickness was denoted in millimeter.

Hardness:

The tablets to be tested are held between a fixed and a moving jaw of hardness test apparatus (Monsanto) and reading of the indicator is adjusted to zero. The screw knob was moved forward until the tablet breaks and the force required breaking the tablet was noted.

Friability:

The friability of tablets were determined by using Roche Friabilator. Twenty tablets were weighed and placed in friabilator and rotated at 25 rpm for 4 min8.Then the tablets were taken out, dusted and reweighed. The percentage friability of the tablets were calculated by the formula,

Percentage Friability = [(Initial Weight – Final Weight)/ Initial Weight] × 100

Weight Variation Test:

Twenty tablets were selected at random and average weight was determined. The individual tablets were weighed and compared with average weight9.Not more than two of the individual weights deviate from the average weight of tablets by more than 7.5% and none should deviate more than 2 times the percentage limit.

Disintegration Time:

The disintegration test was carried out at 37±20C in 900 ml distilled water using disintegration test apparatus10. One tablet was placed in each of the six tubes of the apparatus containing distilled water. One disk was added to each tube. The time taken in sec for complete disintegration of the tablets with no mass remaining in the apparatus was noted.

Estimation of Drug Content:

From each formulation of Aceclofenac tablets, 10 tablets were collected randomly and powdered11. A quantity of powder equivalent to 100 mg of Aceclofenac was transferred into a 100 ml standard flask, dissolved in 10 ml methanol. The volume was made up to 100 ml using phosphate buffer pH 6.8. From this stock solution 10µg/ml solution was prepared. The drug content was estimated by measuring the absorbance of the solution at 275 nm using UV- Visible double beam spectrophotometer against phosphate buffer pH 6.8 as blank.

Wetting Time and Water Absorption Ratio:

Twice folded tissue paper was placed in a Petri dish having an internal diameter of 5 cm containing 6 ml of water. A weighed tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time12. Water absorption ratio (R) was determined by the formula:

$R = 100 \times (Wa - Wb)/ Wb$

Where Wb-Weight of the tablet before wetting, Wa- Weight of the tablet after wetting.

In Vitro Drug Release Study:

In vitro release of Aceclofenac was studied using USP II dissolution apparatus, with 900 ml of dissolution medium maintained at 37±1°C at 50 rpm. Phosphate buffer pH 6.8 was used as a dissolution medium. 1 ml of the samples were withdrawn at suitable time intervals of 5, 10, 15, 30 and 45 min and are replaced by fresh quantity of dissolution medium. The collected samples after suitable dilution were analyzed spectrophotometrically at 275 nm against phosphate buffer pH 6.8 as blank and percentage drug release was determined13.

RESULTS AND DISCUSSION:

Fast dissolving tablets of Aceclofenac using crospovidone (F1) and crosscarmellose sodium (F2) as superdisintegrants and a control formulation F3 (without Superdisintegrant) were prepared by direct compression method. The formulations were evaluated for pre compression parameters and post compression parameters.

Precompression Parameters:

The values of precompression parameters evaluated were found to be within the prescribed limits and indicated good free flowing property (Table 2).

Table No.2 Pre compression Parameters

Formulation code	Angle of repose (□)	Bulk density (g/cm3)	Tapped density (g/cm3)	Compressibility index (%)	Hausner's ratio
F1	32.42+0.65	0.510+0.04	0.581+0.02	12.22	1.14
F2	32.98+1.16	0.512+0.08	0.592+0.06	13.51	1.16
F3	33.44+1.12	0.492+0.12	0.554+0.16	11.83	1.13

***All the values are expressed as mean+ SD; n=3**

Infra-red spectroscopy was used as means of studying drug – excipient compatibility and confirmed by comparing undisturbed structure of IR spectra of Pure Aceclofenac with Aceclofenac containing highest proportion of superdisintegrant. It showed that IR spectrum of pure Aceclofenac and Aceclofenac containing highest proportion of superdisintegrant were similar fundamental peaks and patterns which indicated no drug excipient interaction (Figure 1 to 5).

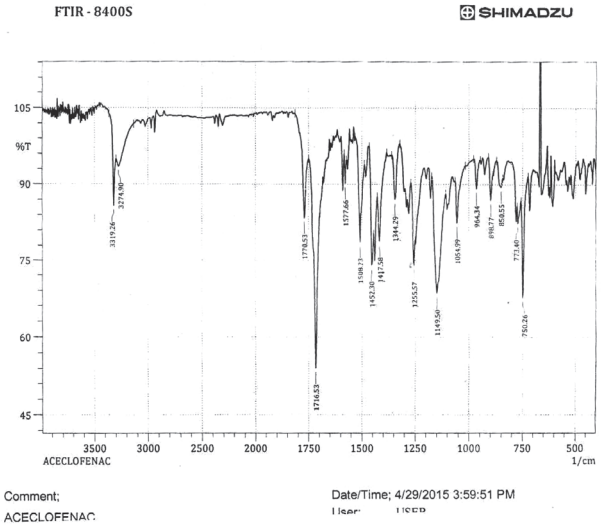


Fig No.1 FT-IR Spectrum of Aceclofenac

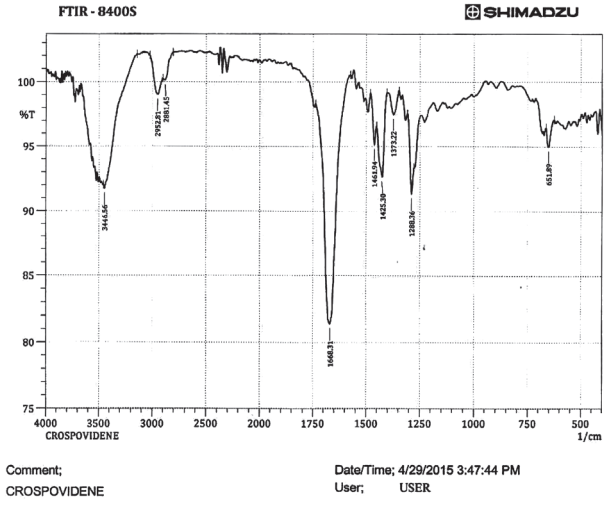


Fig No.2 FT – IR Spectrum of Crospovidone

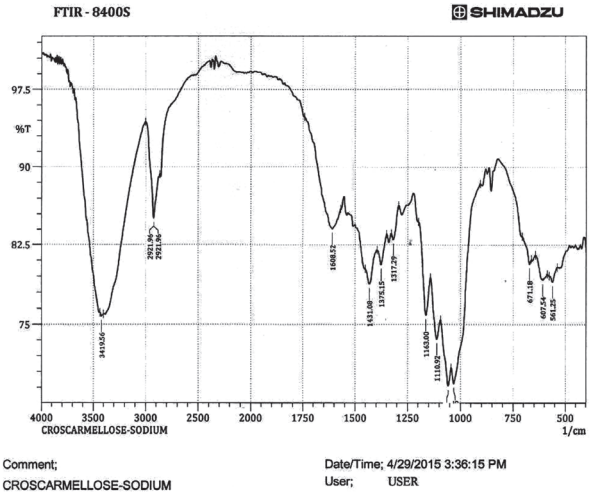


Fig No.3 FT – IR Spectrum of Crosscarmellose Sodium

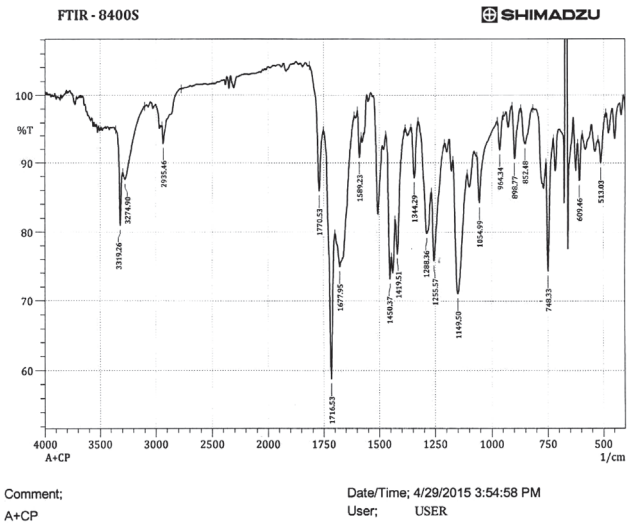


Fig No.4 FT – IR Spectrum of Aceclofenac + Crospovidone

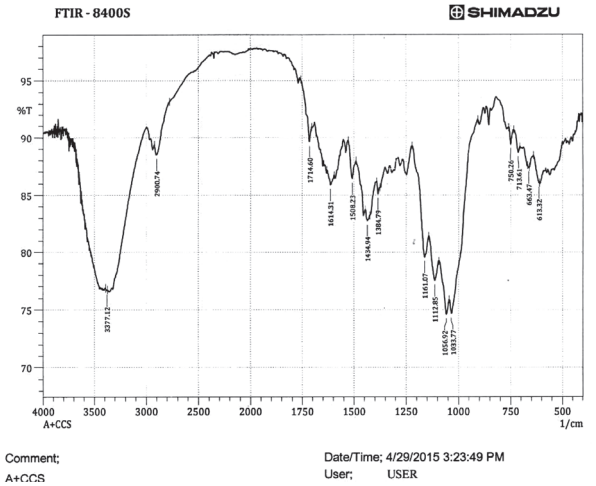


Fig No.5 FT – IR Spectrum of Aceclofenac + Crosscarmellose Sodium

Post Compression Parameters:

The thickness and the hardness of Aceclofenac tablet formulation F1, F2 and F3 were found to be 4.14+0.02, 4.1+0.02 and 4.12+0.04mm and 3.6+1.04, 3.8+1.1 and 3.6+1.32kg/cm2 respectively. All the formulations showed uniform thickness and hardness. Friability test was carried out using Roche friabilator. A maximum weight not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable. The friability values of Aceclofenac tablet formulation F1, F2 and F3 were found to be 0.75+0.56%, 0.63+0.66and 0.84+0.57%. The results revealed that all the formulations of Aceclofenac tablets passed the friability test. In weight variation test twenty tablets of each formulation were selected randomly and weighed. The actual weight of one tablet is 200 mg. So the acceptable deviation was +7.5%. The weight variation of Aceclofenac tablets was found within the range of 197.6+ 1.3 to 202.4+1.6 mg. These results revealed that the tablets obtained were of uniform weight (due to uniform die fill) with acceptable variation as per IP specifications (i.e.) below 7.5%. Tablets were evaluated for disintegration time in the disintegration test apparatus. The disintegration time of Aceclofenac tablet formulation F1, F2 and F3 were found to be 34+1.34, 36+1.12 and 184+2.6 sec. Formulation F1 showed less disintegration time compared to formulation F2 which may be due to the presence of crospovidone as superdisintegrant. The drug content of formulation F1, F2 and F3 were found to be 99.67+2.6, 99.23+1.7 and 99.34+2.4%. The drug content was found to be uniform in all formulations and was within the acceptable limit. The wetting time of formulation F1, F2 and F3 tablets were found to be 28+2.8, 34+1.6 and 86+2.6 sec. The wetting time was considerably reduced in tablets containing crospovidone and crosscarmellose sodium as superdisintegrant compared to formulation F3 without superdisintegrant. The water absorption ratio of formulation F1, F2 and F2 was found to be 76.2+1.36, 72.36+2.36 and 51.25+2.3%. Formulation F1 showed good water absorption ratio due to its swelling capacity. The results of thickness, hardness, friability, weight variation, disintegration time, drug content, wetting time and water absorption ratio of Aceclofenac tablets are given in Table 3.

Table No.3 Post Compression Parameters

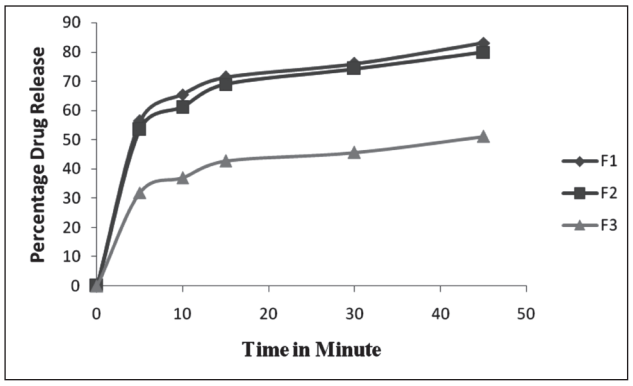
Formulation code	Thickness (mm)	Hardness (Kg/cm2)	Friability (%)	Weight variation (mg)	Disintegration time (sec)	Drug content (%)	Wetting time (sec)	Water absorption ratio %
F1	4.14+0.02	3.6+1.04	0.75+0.56	199.4+1.9	34+1.34	99.67+2.6	28+2.8	76.2+1.36
F2	4.1+0.02	3.8+1.1	0.63+0.66	201+1.4	36+1.12	99.23+1.7	34+1.6	72.36+2.36
F3	4.12+0.04	3.6+1.32	0.84+0.57	202.4+1.6	184+2.6	99.34+2.4	86+2.6	51.25+2.3

***All the values are expressed as mean + SD; n = 3**

In vitro Drug Release Studies:

The percentage drug release from formulation F1, F2 and F3 at the end of 45 min was found to be 83.04+¬1.9%, 79.92+0.78% and 51.12+1.7%, respectively. Formulation F1 prepared by using crospovidone as superdisintegrant showed a better percentage of drug release when compared to formulation F2 prepared using crosscarmellose sodium and F3 prepared without superdisintegrant. This may be due to easy swelling ability and wicking capacity of crospovidone when compared to crosscarmellose sodium. Due to the presence of superdisintegrant, water uptake is good, hence water absorption ratio is high, there by leading to faster disintegration in formulation F1 and F2 compared to F3. The delayed drug release of formulation F3 prepared without superdisintegrant may be due to longer disintegration time and lesser solubility in the dissolution medium. The drug release profiles of Aceclofenac tablets are shown in Figure 6.

Fig No.6 In vitro Release Profiles of Aceclofenac Formulations



CONCLUSION:

Aceclofenac is practically insoluble in water and peak blood level reaches between 1 to 3 hours after oral administration. Hence, an attempt was made to improve the dissolution of Aceclofenac through the formulation of Fast-dissolving tablets with appropriate mechanical strength, which would disintegrate in oral cavity, in less than 30 seconds and would provide an immediate relief from pain due to its faster dissolution in gastrointestinal tract.

The results of experimental studies of Aceclofenac formulations proved that the Powder blend of Aceclofenac showed good flow properties, tablet evaluation tests are within the acceptable limits, IR spectral analysis proved that there was no drug- excipient interaction. The formulation prepared with crospovidone as superdisintegrant showed a rapid drug release than formulation prepared with crosscarmellose sodium and control formulation (without superdisintegrant) and satisfied all the criteria for fast dissolving tablets. The results of the above study clearly indicated that Aceclofenac can be formulated as fast dissolving tablets using crospovidone and crosscarmellose sodium as superdisintegrant in the concentration of 5%w/w by direct compression method. Among all formulations of Aceclofenac FDTS formulation F1 prepared by using crospovidone as a superdisintegrant showed rapid drug release and satisfied all the criteria for fast dissolving tablet.

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Physicochemical Evaluation For Leaves of *Bauhinia tomentosa & Milliettia pinnata*

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ABSTRACT

Plants of Mother nature offers endless source of incredible biomolecules with therapeutic potentials. The present study unveils physicochemical parameters of *Bauhinia tomentosa & Milliettia pinnata* to identify the adulterants and to improve the quality of the plant. This evaluation can also be used as a diagnostic tool for proper identification of the plant.

Key words: *Bauhinia tomentosa, Milliettia pinnata*, Physiochemical parameters, limit tests.

INTRODUCTION

Bauhinia tomentosa & Milliettia pinnata are the medicinal plants indigenous to Asia and Africa. The stem and root extracts of this medicinal plant possess antimicrobial activity1, for the treatment of skin infections & anti-ulcer property. From the literature survey, it is clearly understood that the physicochemical evaluation of Bauhinia tomentosa & Milliettia pinnata was not carried out. The present study is taken up for the physicochemical evaluation for leaves of Bauhinia tomentosa & Milliettia pinnata.

Plant material:

The Plants, Bauhinia tomentosa & Milliettia pinnata were collected from, Tirupati and were authenticated by the Department of Botany, S.V.University, Tirupati. The Voucher Specimens of these plants were preserved in the herbarium of the Department of Pharmacognosy, Sri Padmavathi School of Pharmacy, Tiruchanoor.

EXPERIMENTAL WORK:

Materials and methods:

Requirements:

Leaf powder, Nessler cylinders, tongs, balance, petri dishes, measuring cylinder, sieve no.60, spatula, funnel, specific gravity bottle, china dish, hot air oven.

Chemicals:

Methanol, chloroform, water, ethanol, pumice powder, potassium hydroxide, 0.5M hydrochloric acid, nitric acid, sodium chloride, potassium sulphate, barium sulphate, silver nitrate, phenolphthalein.

Determination of acid value2 :

Definition of acid value:

Acid value is defined as the number which express in milligrams, the amount of potassium hydroxide necessary to neutralize the free acids present in 1 gm of the sample.

Procedure:

Weigh accurately 10 gm of the sample and dissolve it in 50 ml of a mixture of ethanol (95%) and 25 ml of ether previously neutralized with 0.1M potassium hydroxide using phenolphthalein indicator.If required, dissolve the sample by heating slowly and using reflux condenser.To the above sample solution, add 1ml of phenolphthalein indicator and titrate with 0.1M potassium hydroxide solution till the appearance of pale pink colour produced after shaking for half minute.

$$\text{Acid value} = 5.61n/w.$$

Where n = ml of 0.1M potassium hydroxide solution required, w = weight of the sample in gm.

Determination of saponification value3:

Definition of saponification value

Saponification value is defined as the number of mg of potassium hydroxide required to saponify the ester in 1gm of sample substance.

Procedure:

Weigh accurately 2 gm of sample and add it to 200ml glass flask fitted with reflux condenser.

Add 25ml of 0.5M ethanolic potassium hydroxide and small quantity of pumice powder and boil for 30 minutes on water bath under reflux.Add 1 ml phenolphthalein solution and titrate immediately with 0.5M hydrochloric acid (x).Take the blank reading by repeating the same procedure (y).

Calculate the saponification value as: Saponification value = 28.05(y-x)/w,

Where w = weight of substance in gm.

Determination of ethanol soluble extractive value4:

Prepare coarse powder of air-dried drug.Take 100ml of ethanol (specified strength) in conical flask.Macerate 5 gm of powdered drug in above conical flask, close the conical flask and keep it for 24 hours.Shake the flask frequently during first 6 hours; allow it to stand for 18 hours. Evaporate 25ml of the filtrate to dryness in a tarred flat bottomed shallow dish.

Dry at 105°C and weigh it. Calculate the percentage of ethanol soluble extractive value with reference to the air drug.

Determination of water soluble extractive value5:

Prepare coarse powder of air dried drug.Take 100 ml of chloroform water in conical flask.

Macerate 5 g powdered drug in the above conical flask, close the conical flask and keep it for 24 hours.Shake the flask frequently during first 6 hours; allow it to stand for 18 hours.

Filter rapidly preventing loss of chloroform.Evaporate 25ml of the filtrate to dryness in a tarred flat bottomed shallow dish. Dry at 105°C and weigh it.Calculate the percentage of water soluble extractive value with reference to the air dried drug.

Determination of ash value6:

Weigh accurately 2 to 3 gm of air dried crude drug in a treated silica dish and incinerate at temperature not exceeding 450°C until free from carbon.Cool the silica dish and weigh.

If a carbon free ash cannot be obtained, exhausted the charred mass with hot water.

Collect the residue on an ash less filter paper, until the ash is white or nearly white, add the filtrate, evaporate to dryness and ignite at temperature not exceeding 450°C. Calculate the percentage of ash with reference to the air dried drug.

Physical parameters:

Bulk density7:

Bulk density = mass of a powder (w) / bulk volume.

Method:

A powder about (60gm) is passed through a standard sieve number 20.A weighed amount is introduced into a 100ml measuring cylinder. The cylinder is fixed on the bulk density apparatus and the timer knob is set (regulator) for 100 tapping. The volume occupied by the powder is noted. For reproducible results, the process of tapings may be continued until concurrent volume is achieved. This final volume is the bulk volume.

True density8:

True density = weight of powder/ true volume of powder.

Method:

The true density of the Bauhinia tomentosa leaf powder and formulations were determined by the liquid displacement method using immiscible solvent (ethyl alcohol) and the true density ($\rho\tau$) was computed (n=3) according to the following equation:

$\rho\tau$ = W1/(W2+W1) –W3 * SG

Where W1 is the weight of powder, SG is the specific gravity of the solvent, W2 is the weight of bottle and solvent andW3 is the weight of bottle, solvent and powder.

Flow properties:

Angle of repose9:

Definition: Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

Tan ɵ = h/r

Method:

A glass funnel is held in place with a clamp on a ring support over a glass plate. Approximately 100g of powder is transferred into the funnel keep the orifice of the funnel blocked by the thumb. As the thumb is removed, the powder is emptied from the funnel.

The distance between the bottle of the funnel stem and the top of the powder pile must be 6.4mm. The angle of the heap to the horizontal plane is measured with a protractor.

The height of the pile (h) and the radius of the base (r) are measured with the ruler.

The angle of repose is thus estimated.

Chemical tests10:

Limit tests:

Test for chlorides:

Test solution: Specified amount of substance (1g) taken and add 1ml of water then add 1ml of nitric acid then diluted to 50ml in nessler cylinder then add 1 ml of silver nitrate solution. The opalescence in the sample and standard solution are compared by keeping the nessler cylinder against proper background and observing side by side.

Standard solution: 1 ml of 0.05842%w/v solution of sodium chloride and add 1ml of nitric acid and dilutes to 50ml in nessler cylinder then add 1ml of silver nitrate solution. The opalescence in the sample in the sample and standard solution are compare by keeping the nessler cylinder against proper background and observing side by side.

Limit test for sulphates:

Test solution: Specified substances (1g) taken then add 2ml hydrochloric acid diluted to 45ml then add 5ml solution of barium sulphate reagent.

Standard solution: 1ml of 0.1089%w/v solution of potassium sulphate then add 2ml of hydrochloric acid and then diluted to 45ml with water add 5ml solution of barium sulphate reagent. The turbidity in the sample and standard solution are compared by keeping the nessler cylinder against proper background and observing side by side.

RESULTS AND DISCUSSION:

From the above observation, Ash value of a drug give an idea of the earthy matter or the inorganic composition and other impurities present along with the drug. The extractive values are useful to evaluate the chemical constituents present in the crude drug and also help in estimation of specific constituents soluble in a particular solvent. The acid value and saponification value are useful to evaluate the quantity of base required to neutralise and saponify the specified quantity of fatty acid present in drug. By determining the physical parameters such as bulk density, true density and angle of repose, the weight, volume of the powdered drug substance and flow property of the powdered drug substance can be identified. By performing the limit tests for chlorides and sulphates, the presence of chlorides and sulphates in the powdered drug substance can be identified. These parameters are helpful and are of great value in the quality control and formulation development. Establishing standards is an integral part of establishing the correct identity and quality of a crude drug. Various physicochemical parameters established can be important in detecting adulteration and mishandling of the crude drug the parameters which are described here can be considered as distinctive characters of these plants and are good enough to authenticate the drug in herbal industry and prevent adulteration. This will also aid in maintaining the quality assurance of the starting material.

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Table 1: Evaluation of Physical Constants in Bauhinia tomentosa:

Sl.no	Physical constants	Percentage w\w/µ/θ
1	Acid Value	78.54
2	Saponification value	140
3	Ash value	78.54
4	Ethanol soluble extractive value	0.68g
5	Water soluble extractive value	0.64g
6	Porosity	0.548
7	Percentage of porosity	
8	Bulk density	0.149g/cm3
9	True density	1.076g/cm3
10	Angle of repose	0.4125

Table 2: Limit tests:

Sl.no	Limit tests	Powdered Drug of Bauhinia tomentosa
1	For chlorides	Present
2	For sulphates	Present
3	For iron	Present
4	For salicylates	Present

Table 3: Microscopical Examination:

Sl.no	Microscopical Examination	Powdered Drug of Bauhinia tomentosa
1	Starch	Present
2	Calcium oxalate crystals	Present
3	lignin	Present

FIGURE I: Bauhinia tomentosa

Table 1 Evaluation of Physical Constants in *Millettia pinnata*

Sl.no	Physical constants	Percentage w\w/µ/θ
1	Acid Value	84.15
2	Saponification value	78.54
3	Ash value	0.39g
4	Ethanol soluble extractive value	0.73g
5	Water soluble extractive value	0.75g
6	Porosity	0.341
7	Percentage of porosity	
8	Bulk density	0.138g/cm3
9	True density	1.568g/cm3
10	Angle of repose	0.391
11	Loss on drying	7.8

Table 2: Limit tests:

Sl.no	Limit tests	Powdered Drug of *Millettia pinnata*
1	For chlorides	Present
2	For sulphates	Present
3	For iron	Absent
4	For salicylates	Present

Table 3: Microscopical Examination:

Sl.no	Microscopical Examination	Powdered Drug of *Millettia pinnata*
1	Starch	Present
2	Calcium oxalate crystals	Present
3	lignin	Present

FIGURE II: Millettia pinnata

CONCLUSION:

The result of the present study may serve as a guide in the selection of plant for further work of isolation, elucidation and pharmacological screening of the active compounds.

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A Retrospective Study on Sepsis and its Management From The Clinical Pharmacy Perspective in a Tertiary Care Hospital

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ABSTRACT

Sepsis is a syndrome characterized by a systemic response to infection that can rapidly lead to death. The objectives of this study was to ascertain the importance of APACHE II scoring system for the prediction of length of stay and mortality rate in sepsis, the most common pathogens causing sepsis and to detect any drug related problems(DRPs). Patients ≥18years admitted with clinical diagnosis of sepsis during September 2013 to September 2014 with all relevant data were randomly selected for the study. 100 profiles were reviewed and of these 69 had expired, Multiorgan dysfunction was the major cause of death. 81% of the DRPs identified were due to inappropriate drug dosing followed by drug interactions 37%, ADRs 17% and 11% were no drug prescribed for the medical condition and miscellaneous DRPs accounted 14% includingduplication of therapy. Sepsis was classified on basis of pathogen and results reflected 57% of sepsis were caused by gram negative bacteria,28% were culture negative, 10% by gram positive bacteria and 3% had mixed growth and 2% were fungi. The APACHE-II scoring system was found useful for classifying patients according to their disease severity with an inverse relationship evident between the score and length of stay, incidence of DRPs,and chances of mortality as well. Establishing an inter-professional collaboration with the involvement of clinical pharmacist in sepsis management can thereby resolve DRPs with the ultimate aim of improving the quality of treatment rendered to the needy.

Key words: sepsis, drug related problems, clinical pharmacist

INTRODUCTION

Sepsis has been around since the dawn of time, having been described for more than 2000 years, although clinical definitions are recent. Sepsis is a syndrome characterized by a systemic response to infection that can swiftly lead to death.1Sepsis is an all-too-common occurrence in hospitalized patients, especially in Intensive Care Units (ICUs). Many factors must be taken into account in the treatment of sepsis, including choice and usage of antibiotics, patient allergies, local sensitivities of pathogens, origin, site, source of infection and so on. In addition to being difficult to manage, sepsis contributes significantly to health care burden and has considerable associated morbidity and mortality concerns.2

Infectious agents are the most emerging causes of febrile illness (30%–40%). Hence, in the first contact with febrile patient doctors often have doubts regarding the etiology of the disease and the need for giving empirical antibiotic therapy. It is an increasingly common cause of mortality and morbidity particularly in elderly, immunocompromised and critically ill patients.

Approximately 25–35% of patients with severe sepsis and 40–55% of patients with septic shock die within 30 days.3

To analyse the severity of sepsis, a scoring system named as “APACHE-II scoring system” was employed. APACHE instrument (Acute Physiology and Chronic health Evaluation) was introduced by William Knaus in 1985 and defined by twelve physiological characteristics which covered most physiologic systems and was called "APACHE II"4. The system is still the most widely used system for the evaluation of ICU patients due to its simplicity in gathering information through regular tests and examinations and reproducibility. The APACHE II system consists of Patients' acute physiological symptoms such as temperature, mean arterial preassure, blood oxygenation, respiratory rate, heart rate, serum potassium level, serum creatinine level, hematocrit, WBC count,Glascow Coma Scale (GCS), age and chronic health problem. The APACHE II is usually measured during the first 24 h of ICU admission; the maximum score is 71. A score of 25 represents a predicted mortality of 50% and a score of over 35 represents a predicted mortality of 80%5. The APACHE II severity score has shown a good calibration and discriminatory value across a range of disease processes, and remains the commonly used international severity scoring system.

Although studies from developing nations are still lacking, and there exist some differences in approaches across studies, the most dominant feature is the consistency of methods and findings. In most countries, about one in ten ICU patients have severe sepsis. The management of patients with severe sepsis and septic shock requires pre-determined antibiotic protocols, elaborated on the basis of evidence available in the literature and local microbiological pattern6.

The main objectives of our study were to ascertain the importance of APACHE II scoring system for the prediction of severity, length of stay and mortality rate in sepsis, the most common pathogens causing sepsis, to compare between early empirical antibiotic treatment and its accuracy with the culture sensitivity report and review patients medical records to detect any drug related problems(DRPs).

Owing to a high mortality in bacteraemia, empirical broad-spectrum antibiotic therapy is to be initiated to cover potentially dangerous pathogenic bacteria. To limit the emergence and spread of antibiotic resistance, broad-spectrum therapy should be narrowed according to the results of blood cultures at the earliest. However, the results of blood cultures are often ignored if the patient is doing well on broad-spectrum therapy.

Drug-related problems are known to be a major problem associated with pharmacotherapy. A broad range of studies, mainly in the area of prescription-only medicines, supports this fact. DRPs have been shown to exist in hospitalized patients. Polypharmacy and increasing age and severity have been identified as important risk factors7. Hence, DRPs causeconsiderable patient morbidity and in some cases death, in addition to the increased health care expenditures.

Studies have shown thedominance of Gram-negative bacterial pathogens as the common cause of sepsis in India which is a contraryto the bacteriologic profile from western nations. Progress has been made over the past half-century in identifying and treating patients with sepsis and decreasing fatality rates. An idea of the common pathogens causative of sepsis gives the healthcare providers an insight into the treatment and enable them to prescribe appropriate antibiotic treatment prior to pathogen identification.

METHODOLOGY:

This retrospective study was conducted in tertiary care referral hospital for a period of one year after getting approval from the ethics committee of the hospital.The patients were randomly selected based on inclusion and exclusion criteria. Patients who were clinically diagnosed as sepsis with age above ≥18 years were included, whereas patients with incomplete data were excluded from the study. The randomization was carried out by the Graph Pad software. Patient’s demographic details and other pertinent data were collected by reviewing electronic medical records and manually maintained medical records wherever necessary. The collected data were transcribed into a specially designed data collection form. The drug therapy of the patients were reviewed and analysed for any drug related problems.The safety, efficacy, outcomes, ADRs, and

other drug related problems were identified based on patient's clinical condition correlating various laboratory parameters."APACHE-II scoring system" was employed to analyse the severity of sepsis

RESULTS:

Out of 100 patients included in the study there was a male preponderance of 77%. Among the study population 69 expired; Multiorgan dysfunction was the major cause of death . Results are shown in table 1

Table 1: Gender and age distribution

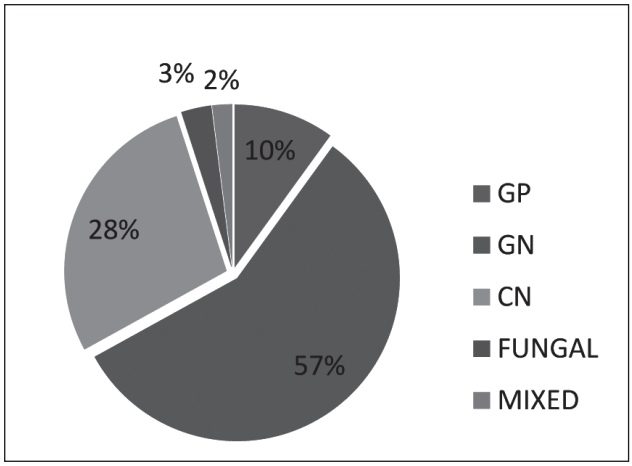
CHARACTERISTICS	NO: OF PATIENTS
GENDER	
Male	77
Female	23
AGE	
18-27	4
28-37	6
38-47	12
48-57	24
58-67	28
68-77	17
78-87	6
88-92	3

Sepsis etiological classification

Out of 100 patients studied 28% cases were culture negative. In the remaining cases gram negative bacteria predominated with 57% followed by gram positive bacteria 10% .But there were mixed infections in 2% cases and fungal sepsis in 3% cases as shown in figure 2. The main pathogens isolated wereKlebsiella pneumoniae, Pseudomonas aeruginosa,Acinetobacter baumannii, Escherichia coli, Enterococcus and Staphylococcus aureus. Regarding the antibiotic susceptibility, Colistin, Linezolid and Vancomycin was found to have more susceptibility against these above mentioned organisms. ESBL positive strains were 45% and MDR pathogens accounted for 39% according to the culture sensitivity reports.

Fig 2: Sepsis classification based on Pathogen.

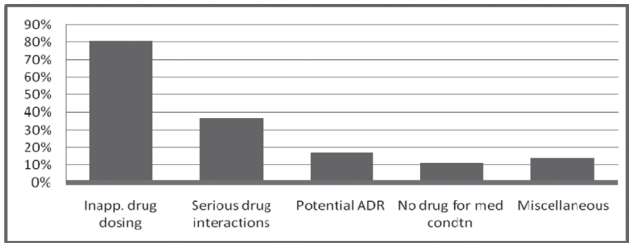
Identification and classification of drps



All the collected data were analysed and the DRPs were identified and the results are shown in figure 3. 81% of the DRPs were due to inappropriate drug dosing, 37%were detected as serious drug interactions, 17% were potential ADRs and no drug was prescribed for existing medical condition accounted11%. Miscellaneous DRPs accounted for 14% which included duplication of therapy and administration errors.

Fig 3: DRP distribution

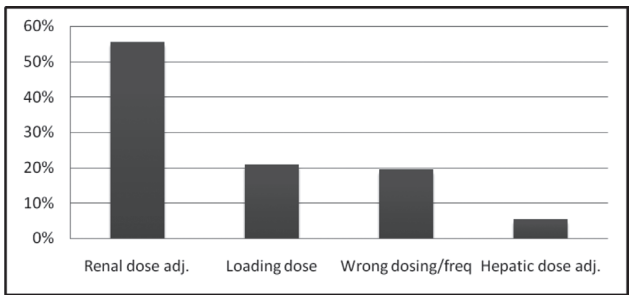
Inappropriate drug dosing was further expanded into its



individual components and is shown in figure 4. Graph given below shows a failure to adjust dosage of drugs in renal failure accounted for 56%, failure to give loading doses of antibiotics were observed in 21% cases, wrong drug dosing or frequency was found in 19% and failure to adjust dosage according to hepatic impairment was 6%.

Fig 4:Inappropriate drug dosing

Adverse drug reactions



Drug induced electrolyte and gastro-intestinal disturbances topped with 25% each, followed by hematologic, endocrine and liver related problems each accounting for 18% each. Results are as shown in table 2.

Table 2: Classification of ADRs observed according to WHO-ART

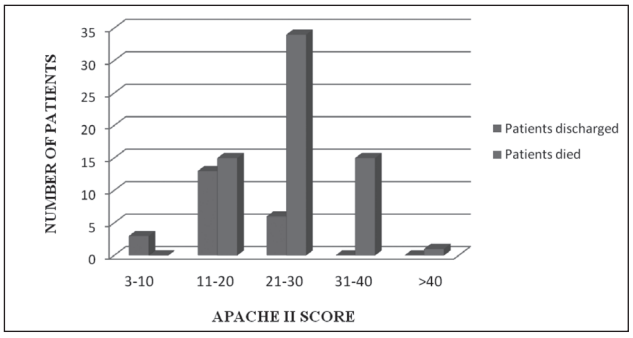
ORGAN SYSTEM AFFECTED	No: OF ADRs
Skin and appendages disorders (0100)	1
Gastro-intestinal system disorders (0600)	4
Liver and biliary system disorders (0700)	2
Metabolic and nutritional disorders (0800)	4
Endocrine disorders (0900)	2
Platelet, bleeding and clotting disorders (1230)	3
Body as a whole- general disorders (1810)	1

Apache score

The severity of sepsis was correlated with mortality by using APACHE Score II and it was found that as the score increased,so did the mortality rates. The results are as presented in the table 3 and patient outcome and APACHE score are plotted in figure 5.

Fig 5:Relationship of APACHE II score with the outcome of patients (n=87)

Table 3: APACHE II score and patients outcome(n=87)



APACHE II SCORE	Number of patients	Patients discharged	Patients died	Observed mortality
3-10	3	3	0	0%
11-20	28	13	15	53.57%
21-30	40	6	34	85%
31-40	15	0	15	100%
>40	1	0	1	100%

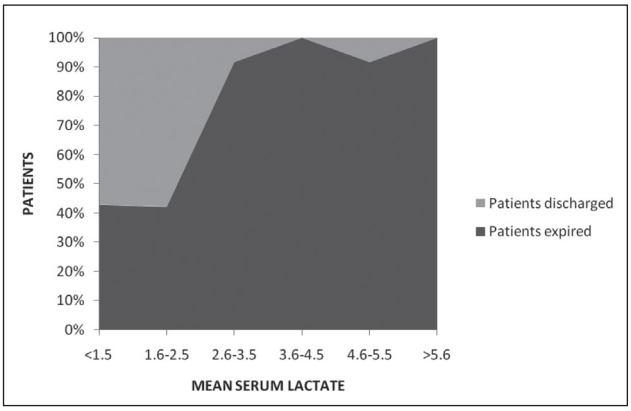
The mean APACHE II score on first 24 hours was 23.28 ± 7.86 and the mean estimated mortality was 47.35% ± 0.23%. The mean 24 hours APACHE II scores and estimated mortality of patients who were discharged was 16.36 ± 5.25 and for those who died was 25.63 ± 7.2.

Serum lactate

Serum lactate was found to be elevated in 59.5% of the patients (n=84) thereby indicating it as a reasonable biomarker in sepsis, especially septic shock and also an indicator of mortality owing to the tissue hypoxia. The correlating graph is given below. Serum lactate is associated with mortality in severe sepsis and septic shock. Hence, this also becomes a potential biomarker to risk stratify patients with severe sepsis. Figure 6 shows a higher mortality with a higher mean serum lactate.

Fig 6: Mean serum lactate vs mortality

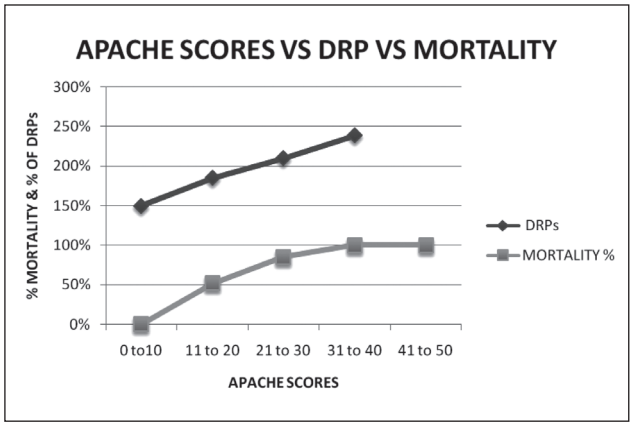
When analysed, there was a positive correlation between



APACHE score, No: of DRPs and mortality rates.

Table 4:Relation between APACHE score, length of stay, DRPs and mortality (n=87)

Apache II Scores	No: of Patients	Mean Length of Stay (Days)	% of Drps	Mortality %
0 to 10	2	22.5	150%	0
11 to 20	29	13.69	185%	51.72
21 to 30	40	10.1	210%	85
31 to 40	15	9.86	239%	100
41 to 50	1	2	0%	100



Finally, the pathogen profile was also studied out of the 100 samples studied, 70% were culture positive bacterial sepsis. From this culture positive samples, 57% samples were from patients infected with gram negative organisms, 10% samples were from patients infected with gram positive bacteria. In the present study, highest causative organism isolated was K. Pneumoniae followed by E. Coli, A.baumannii, Pseudomonas aeruginosa, Enterococcus and S.aureus.

DISCUSSION:

Patients admitted in intensive care unit with sepsis are critically illand need prolonged and continuous care. Many measureshave been used successfully including APACHE II. But it has not been shown whether these tools would correlate with the amount of DRPs encountered. It is quite natural that as the severity of sepsis increases, more aggressive pharmacotherapeutic management becomes a necessity. This is useful for analysing the future prognosis of the outcomes and prevention of badoutcomes.

Our study provides the mean scores for twooutcomes (discharged and alive) that would preliminary provide the researchers to develop exact cut offs ofprediction. Ourstudy results had similar mean APACHE score studies conducted by Fakhir raza et al8. A higher mean APACHE score may be an indication of the severity of the cases as the study was conducted in a tertiary care referral hospital. Thus the meanAPACHE scores clearly shows the critical nature of our admitted patients.

Another interesting result found was that a simultaneous increase in APACHE scores and a gram negative infection results in a higher mortality rate. Gram-negative bacteria have often been implicated in the pathogenesis of severe sepsis and septic shock due to their ability to trigger the shock pathway and is evident from the study of Munford R S9. However, patients with clinically suspected gram negative sepsis but without microbiological documentation and patients with documented infection share common risk factors and are at similarly high risk of death. This study suggests that the optimal therapy in gram negative septicemia is inevitable as greater is the risk of going into septic shock.

Mean length of stay was found to be 12.04 days in general. A further stratification based on the sepsis severity will throw much light into the variations in the length of stay.Greater severity of illness recorded by the APACHE score was associated with longer lengths of stay in the hospital and ICU.

Mean serum lactate was associated with mortality independent of clinically apparent organ dysfunction and shock in patients admitted to the ICU with sepsis. A mean serum lactate level of≈ ≥2.5 mmol/L showed a rapid increase in mortality and a mean lactate level of ≈ ≥4 mmol/L showed more than 90% mortality. Shapiro Nathan et al10 has shown the significance of using lactate as a risk-stratification tool.

Sepsis and septic shock have been produced by all species of aerobic and anaerobic bacteria. Gram negative bacilli were found to be the most common cause of sepsis and septic shock. Gram negative organisms commonly isolated were Klebsiella, E.coli, Acinectobacter and Pseudomonasaccounting for 57%. Gram positive organisms commonly observed were Enterococcus and S.aureusaccounting for 10%. These results are contradictory to a study conducted by Florian B Mayr et al11 which affirms that gram positive organisms predominate in sepsis.

Initial antimicrobial therapy was inappropriate in almost 35 episodes (35% of culture-positive episodes). De-escalation was not possible in a majority of cases due to resistance patterns and severity, instead antibiotic escalation was done in most cases Thus de-escalation may practically be possible only in a few cases of septicemia.

The significant increase in resistance pattern of E.coli, K.pneumoniae Acinectobacter, Pseudomonas, Enterococcus and S.aureus pathogens probably reflects the rise of ESBL in the community which is evident from the culture sensitivity reports indicating a total of 45% ESBL positivity and 39% of MDR isolates. However it should be underscored that MDR Gram-negative species of K.pneumoniae,E.coli, A.baumannii, P.aeruginosapredominate in many cases although gram positive organisms showed some ESBL positivity. These findings suggest that initial empirical antibiotic therapy of sepsis with Gram-negative as well as Gram-positivecoverageshould rely on the local sensitivity patterns.

The main objective of the study was to ascertain the potential role of clinical pharmacist in sepsis. DRPs were analysed and were classified into 5 major classes. Inappropriate drug dosing of atleast one drug was found in 81% of the cases; majority of them being failure to give loading doses of antibiotics or incorrect dosing such as for Teicoplanin, Tigecycline, Meropenem and Colistin; inaccurate dosage adjustment in renal and hepatic impairment cases especially for antibiotics. The research work by JA Roberts et al13discussed the altered pharmacokinetic properties of antibiotics in critically ill patients; essentially sepsis patients. Using the antibiotic pharmacodynamic bacterial kill characteristics, altered dosing regimens can be devised that also account for such pharmacokinetic change. Knowledge of antibiotic pharmacodynamic properties and the potential altered antibiotic pharmacokinetics in sepsis patients can allow the intervening person to develop individualized dosing regimens. Specifically, for renally cleared drugs, measured creatinine clearance can be used to drive many dose adjustments.

Drug interactions of Category D and Category X accounted for 37% cases.No drug order for medical condition accounted for 11%. 17% of the DRPs accounted for potential ADR identified within the limitations of a retrospective study.

We also identified potential risk factors for the administration of inadequate antimicrobial treatment of infections including increased number of DRPs, severity of illness, and patient age. The significance of these findings are that they may help to explain, at least in part, the increased in hospital mortality observed in sepsis patients. More importantly, these data could help to improve existing strategies for the treatment of sepsis among critically ill patients.

This study describes the trends of DRPs and pathogens in sepsis arising in a tertiary care referral hospital in south India.Based on our experience from this investigation, and a review of the available medical literature, we have developed several recommendations aimed at the avoidance of DRPs, inadequate antimicrobial treatment for sepsis patients. It appears that formulation of a sepsis team with the inclusion of a clinical pharmacist will help to tackle the problems associated with antimicrobial therapy, critical care pharmacotherapeutic management, in the early course of infection especially prior to the development of severe sepsis and septic shock.

This is the pioneer clinical pharmacy study, to our knowledge, that provides clinical and microbiological characteristics of well-documented cases of sepsisin an advanced tertiary care centre in India. The study was not interventional for the implementation. It may be hypothesized that the decrease of DRPs in sepsis may be linked with a decreased rate of mortality and improved patient outcomes. There are only few studies on the impact of clinical pharmacist in sepsis management even from Western counterparts.

LIMITATIONS:

Our study was done as a pilot study as we were unable tofind sufficient data addressing this particular setting in India.Furthermore, we could only calculate the APACHE scores of 87 patients out of the 100 samples because data was insufficient for calculation. DRPs were not classified according to any standard classification system. Also the whole diagnostic data was documented by the clinical pharmacy professionals and hence the results may vary slightly from a clinicians view point. Serum Procalcitonin level ,which happens to be a major specific marker of sepsis were not recorded for most of the patients for accurate diagnosis. Moreover, tedious statistical techniques were not employed to project the results.

CONCLUSION:

Although the compliance rate with empiric protocols was good, in many bacteraemic episodes blood culture results and antibiotic sensitivity profiles showed increasing resistance to even reserved antibiotics leading to higher mortality and excessive use of expensive broad-spectrum antibiotics. Our results show that the APACHE II scoring system is a very useful instrument in predicting the mortality rates in patients who are in more need of care. Our study provides the mean scores for two outcomes (expired and discharged) that would preliminary provide the clinical pharmacist with an idea of the expected DRPs and ways to tackle them.

Antibiotic de-escalation is regarded as a well-tolerated and highly recommended approach in critically ill patients with sepsis. But the available data suggest that there is practical difficulties in de-escalation due to the emergence of resistance and severity patterns. Empirical therapy guidelines can be prepared by taking into account the sensitivity patterns, and regular updation of antibiograms

The results of our study underscore the importance of implementing clinical pharmacy services to this population that are at a higher risk of mortality. Aggressive and timely preventive and intervention strategies for this cohort of patients would substantially improve clinical and economic outcomes. Thus,we conclude that the involvement of a clinical pharmacist as a part of the team rounds is necessary and can help detect and prevent DRPs thus reducing mortality risks and thereby improving patient outcome.

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