Journal of Pharmaceutical and Biological Sciences
ISSN: 2320-1924; CODEN: JPBSEV

Available online at: http://www.jpabs.org/
Original Article

A study to evaluate the effect of dosing time of deriphyllin retard as bronchodilator in asthma patients

Beere Nagaraju[1], Vanaja K[1], Neethu Sara George[1], Revadi SS[2], Mohammadreza Kianibakiani[1]

[1]Department of PharmD & Clinical Pharmacy Practice, Visveswarapura Institute of Pharmaceutical Sciences, Bangalore -560070.
[2]Department of Pulmonary Medicine, KIMS Hosital & Research Centre, Bangalore-560002.

Received: 18-03-2017 / Revised Accepted: 25-04-2017 / Published: 26-04-2017

ABSTRACT

The present study was performed on outpatients at the Department of Pulmonary Medicine, KIMS hospital and research centre, diagnosed with mild to moderate persistent bronchial asthma as per the guidelines of Global strategy for diagnosis and prevention of bronchial asthma. With the clearance from IEC, VIPS, patients who gave the informed consent fulfilling the inclusion/exclusion criteria were included in the study. The main aim of the study was to compare the effect of morning dosing versus evening dosing of Deriphyllin retard, which has been reported to exhibit circadian variation. Demographic data including the age, sex, weight, height, occupation, educational status, family history, region of stay was recorded. Patients were advised to take Deriphyllin retard orally, either in morning or evening based on the group in which they were included. Group A consisted of patients who were advised to take morning dose of Deriphyllin, and group B consisted of patients who were advised to take evening dose of Deriphyllin retard. Efficacy of Deriphyllin was assessed by pulmonary function test (Spirometry) parameters such as Forced Expiratory Volume per Second (FEV1); Forced Vital Capacity (FVC); FEV1/FVC ratio. Spirometry test was performed for all patients in both groups at baseline and follow-up on the 5th day. FEV1 was found to be increased to a higher extent when Deriphyllin Retard was administered in the evening. The FEV1/FVC ratio defines the presence of airway obstruction to be present when it is less than 0.75 [according to American Thoracic Society) and less than 0.70 (according to British Thoracic Society]. In the present study the FEV1/FVC was found to 0.769±0.178 after morning dose and 1.01±0.42 after evening dose, which indicates that the evening dose is more efficient in comparison to morning dose. Hence we can conclude that in our study population evening dose would be a better option in comparison to morning dose for treatment with Deriphyllin Retard.

Keywords: Deriphyllin, Asthma, Dosing time, Morning, Evening, Comparison.

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. These episodes are usually associated with variable widespread airflow obstruction within the lung that is often reversible either spontaneously or with the treatment[1-3]. Asthma is a seriously growing health problem, especially in the developing country like India and India has approximately 15-20 million asthmatics, with a median prevalence of about 2.4 per cent in adults of over 15 year of age (1.69-3.47)[4-5]. The Bangalore population had a higher prevalence of asthma compared to Delhi, Kanpur and Chandigarh[6]. Asthma was the tenth most common diagnosis in emergency department visits, and as of 1996, it was ninth most frequent diagnosis seen Out-Patient Department (OPD). Due to modern lifestyle, urbanization, and industrialization dust and dust products have become part of modern life. Along with this the sensitivity of the humans towards the pollens has made individuals more prone to asthma attacks[7]. Management of Asthma is to achieve and maintain clinical control. There are the drugs used in the treatment of Asthma for

***Corresponding Author Address:** Dr Nagaraju B, Visveswarapura Institute of Pharmaceutical Sciences, Bangalore -560070, India; -mail: nagaking2001@yahoo.com*

effective control of acute attacks and in the long term prevention of further episodes and airway renovation in early stage. These drugs are classified as Bronchodilators which relieves bronchospasm (Relievers) and Anti-inflammatory drugs for prevention of bronchospasm (Controllers). Relievers include inhaled β_2 agonists and anticholinergics, short acting oral β_2 agonists and theophylline for providing rapid relief from an asthma attack by quickly opening up the narrowed airways and Controllers include inhaled and systemic corticosteroids, theophylline, cromones and anti-Ig E antibodies and anti-leukotrienes for reducing the inflammation in the airways that occurs in asthma[8,9].

Methylxanthines like theophylline, aminophylline, doxophylline and diprophylline constitute non-selective phosphodiesterase (PDE) inhibitors and these are characterized by mild bronchodilator, immunomodulator, anti-inflammatory, mucoregulatory, bronchoprotective, steroid sparing and inflammatory cell stabilizing properties[10,11].

Theophylline [1H-Purine-2,6-dione, 3,7-dihydro-1,3-dimethyl] Pharmacokinetic studies have reported circadian variation in the past. Chronotherapy of theophylline in nocturnal asthma studied showed that evening dose of theophylline can be prophylactically used. Theophylline and Etophylline is used to prevent and treat wheezing, shortness of breath and difficulty in breathing caused by asthma, chronic bronchitis, emphysema, and other lung diseases. However the use of theophylline is often restricted by its narrow therapeutic range. Etophylline is a bronchodilator and normally applied in combination with theophylline. It relaxes and opens air passages in the lungs, making it easier to breathe. The pharmacological actions of Etophylline are generally considered like those of theophylline. Unlike other xanthine derivatives, Etophylline does not convert into theophylline in the body. This offers a wide therapeutic window and combination of Etophylline and Theophylline exhibits less frequent adverse side effects than an equivalent dose of theophylline alone[12].

Theophylline in combination of Etophylline is available as the branded product of Deriphyllin. Deriphyllin is most commonly prescribed for mild to persistent asthma and it is available as injection (Each 2ml contains etophylline 84.7mg and theophylline 25.3mg) and tablets (plain contains etophylline 77mg and theophylline 23mg; retard 150mg contains etophylline 115mg and theophylline 35mg and retard 300mg contains etophylline 230mg and theophylline 70mg). However, literature related to the chronotherapeutic effect of this combination is not reported. Retarded release tablet of Deriphyllin is prescribed as once a day dosing in mild to persistent asthma patients, but, the circadian variation of Deriphyllin based on the time of dosing is not known. Therefore, the present study is being aimed to evaluate the effect of time of dosing (morning dosing versus evening dosing) of Deriphyllin in asthma patients.

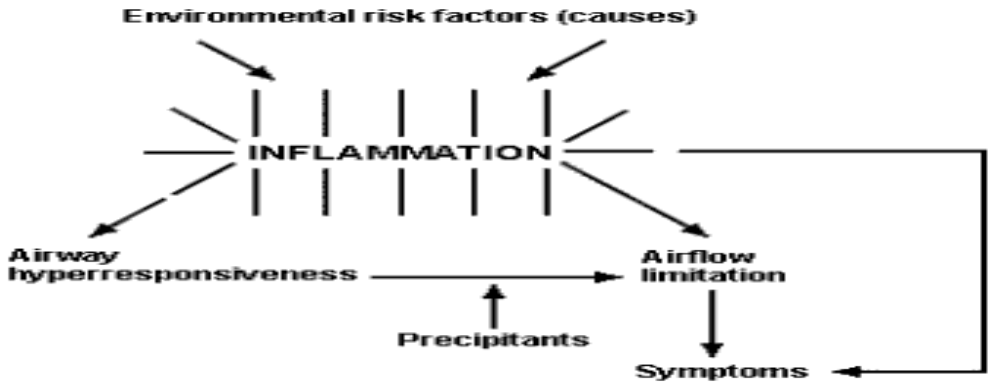


Fig 1: Mechanism underlying the definition of Asthma

MATERIALS AND METHODS

Methodology is a systematic and coordinated way to solve research problems. Research methodology involves the systematic procedure by the researcher, which starts from initial identification of problem to its final conclusion. The study conducted was to evaluate the effect of time of dosing (morning dosing versus evening dosing) of Deriphyllin in asthma patients. This chapter deals with description of methodology has been discussed under the following headings: research design, study site, study criteria, source of data, study period and procedure for data collection and data analysis plan.

Research Design: Hospital based prospective and comparative study.

Sample Design: Random Sampling

Sample Size: 08 patients diagnosed with mild to moderate persistent bronchial asthma.

Study Site: Department of Pulmonary Medicine of Kempegowda Institute of Medical Sciences (KIMS) Hospital, 810 bedded tertiary care teaching hospital situated at central Bangalore.

STUDY CRITERIA:

Inclusion Criteria: Patients who have been diagnosed of mild to persistent asthma aged above 18 years.

Exclusion Criteria:

- Patients who are on any other bronchodilator therapy in previous 48 hours
- Patients who are on steroids (all routes of administration)
- Patients who refuse to participate in this study
- Paediatrics patients / pregnant women/ lactating mothers
- Patients who are already on theophylline to the past 12 hrs.

Study Period:

The study was conducted for a period of three months.

Source of data:

Patients with mild to moderate persistent bronchial asthma attending Pulmonary medicine Out Patient Department of Kempegowda Institute of Medical Sciences Hospital and Research Centre.

Ethical Committee Approval: Institutional Ethical Committee clearance was obtained from KIMS Hospital and Research Centre, Bangalore to carry out the present study (vide: Letter No: VIPS/2014/5, Dated 19th Feb. 2014))

Method of data collection and data analysis plan: After obtaining approval and clearance from Institutional Ethics Committee (IEC), a hospital based prospective comparative study was conducted for 6 months on outpatients of the Pulmonary Medicine of KIMS hospital, Bangalore. The patients who satisfied the study criteria were included in this study by obtaining informed consent. Demographic data was collected from the eligible patient's case sheet which includes age, gender, body weight, Height, family history, education, region where the subjects are staying and occupation.

Relevant laboratory investigations were done at the beginning and at the end of the study.

Patients were grouped as:

Group A = Patients who were advised to take Deriphyllin retard medication in the morning and Group B = Patients who were advised to take Deriphyllin retard medication in the evening.

From both the groups, the asthma symptom score was collected at the baseline. Pulmonary function tests (Spirometry) parameters were recorded at the baseline and follow-up on the 5th day, parameters recorded were:

Comparison of Forced Expiratory Volume per second (FEV1), Forced Vital Capacity (FVC) and Forced Expiratory Volume per second/ Forced Vital Capacity (FEV1/FVC) between morning and evening dosing.

RESULTS

A prospective study was aimed to evaluate the effect of dosing time of a bronchodilator (Deriphyllin Retard) in asthma patients. We have included 8 patients in our study, 4 patients received Deriphyllin as morning dose and 4 patients received Deriphyllin as evening dose.

Table 2: Gender distribution

Gender	Morning Dose		Evening Dose	
	Number	Percentage (%)	Number	Percentage (%)
Male	4	100	2	50
Female	0	0	2	50
Total	4	100	4	100

Figure 2: Bar diagram showing gender distribution

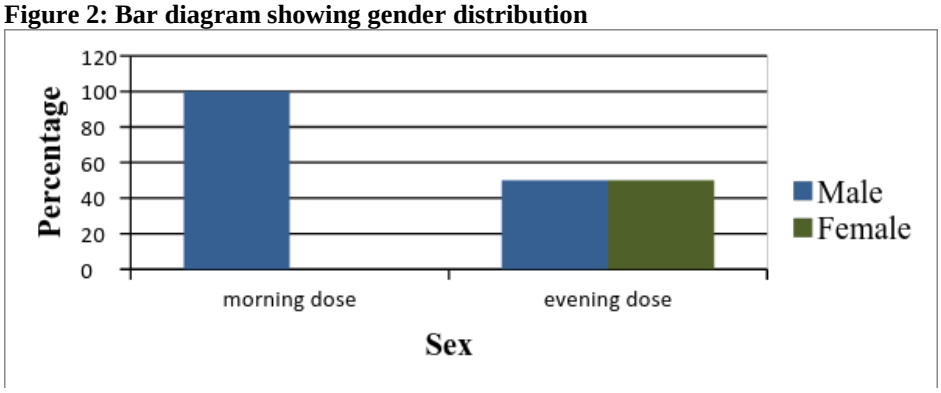


Table 3: Age distribution

Age of the Patients(years)	Morning Dose		Evening Dose	
	Number	Percentage (%)	Number	Percentage (%)
18-24	1	25	1	25
25-31	2	50	1	25
32-38	0	0	0	0
39-45	0	0	0	0
46-52	0	0	1	25
53-59	1	25	1	25
Total	4	100	4	100
mean age± SD	34±15.11 years		37.5 ±15.11 years	

Figure 3: Bar diagram showing age distribution

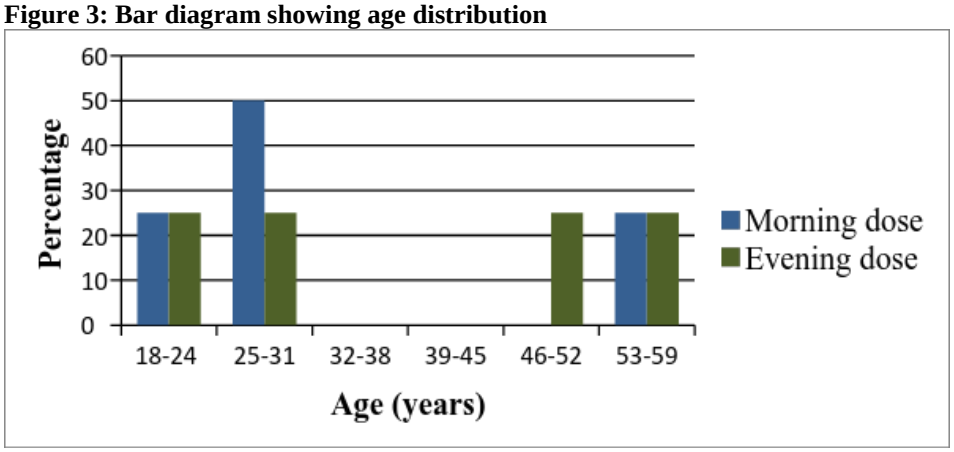


Table 4: Distribution on weight

Weight (kg)	Morning Dose		Evening Dose	
	Number	Percentage (%)	Number	Percentage (%)
40-54	2	50	2	50
55-69	1	25	1	25
70-84	0	0	1	25
85-99	1	25	0	0
Total	4	100	4	100
Mean weight ±SD	64.25±18.97 kgs		54.5±18.97 kgs	
Overall mean weight	59.38			

Figure 4: Bar diagram showing weight distribution

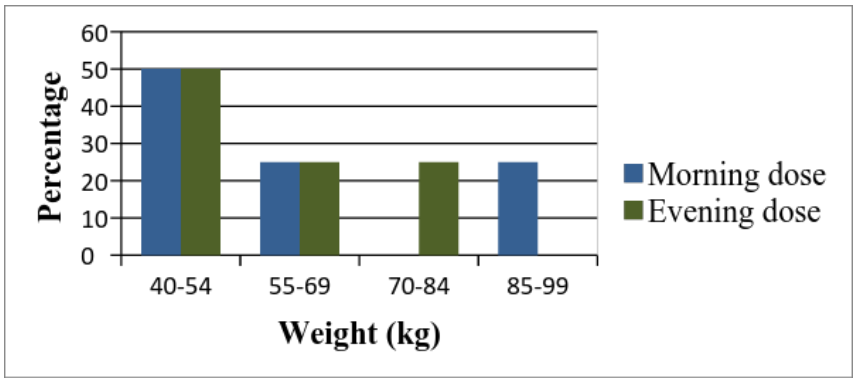


Table 5: Height distribution

Height (cms)	Morning Dose		Evening Dose	
	Number	Percentage (%)	Number	Percentage (%)
150-154	0	0	1	25
155-159	1	25	1	25
160-164	1	25	0	0
165-169	1	25	0	0
170-174	1	25	1	25
175-179			1	25
Mean height±SD	165.5 ±9.26 cms		164.5±9.26 cms	

Figure 5: Bar diagram showing distribution of height

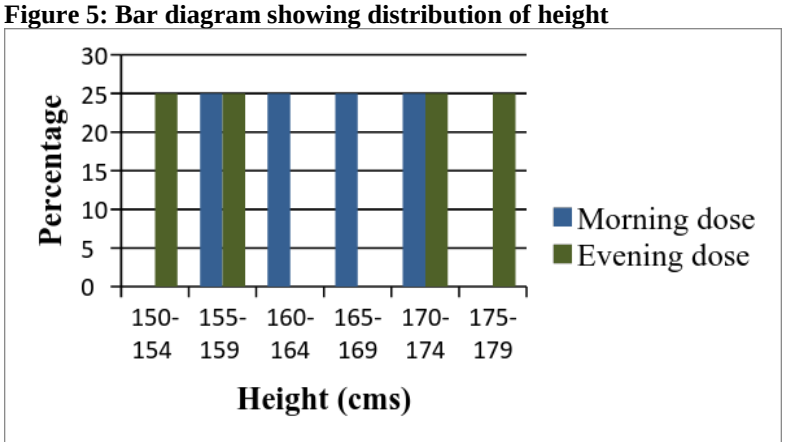


Table: 6 Distribution based on occupation

Occupation	Morning Dose		Evening Dose	
	Number	Percentage (%)	Number	Percentage (%)
Student	1	25	1	25
Housewife	0	0	1	25
Working	3	75	2	5
Total	4	100	4	100

Figure 6: Bar diagram showing distribution of occupation

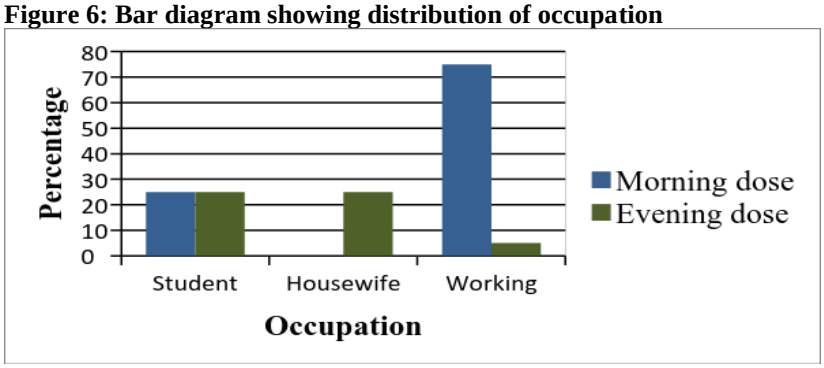


Table 7: Educational status

Education	Morning Dose		Evening Dose	
	Number	Percentage (%)	Number	Percentage (%)
Illiterate	0	0	2	50
Primary (up to SSLC)	3	75	0	0
Higher Secondary (PUC)	0	0	2	50
Degree	1	25	0	0
Total	4	100	4	100

Figure 7: Bar diagram showing educational status

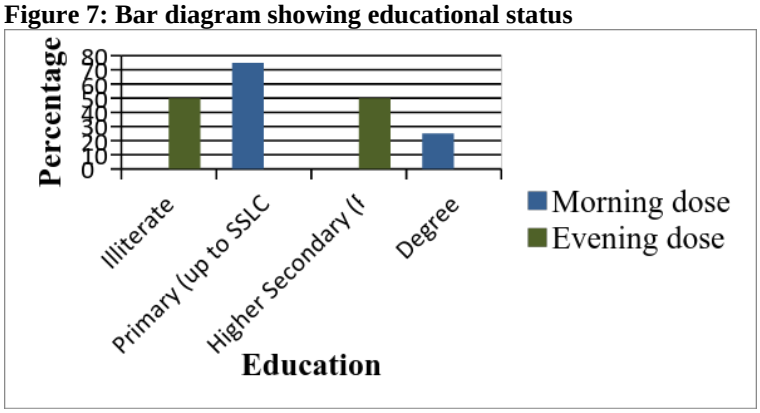


Table: 8 Family history of asthma

Family History	Morning Dose		Evening Dose	
	Number	Percentage (%)	Number	Percentage(%)
Not Sure	3	75	2	50
Present	1	25	2	50
Total	4	100	4	100

Figure: 8 Bar diagram showing family history of asthma

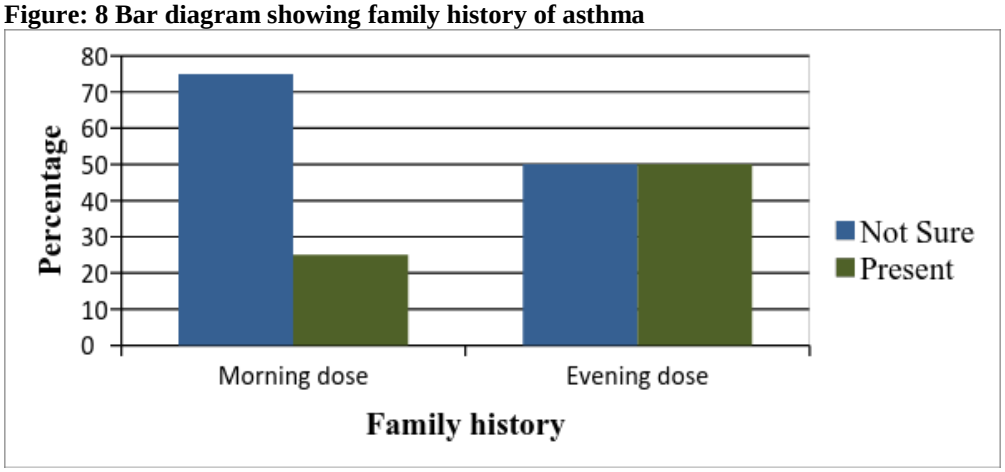


Table 9: Distribution based on region of stay

Region	Morning Dose		Evening Dose	
	Number	Percentage (%)	Number	Percentage (%)
Rural	2	50	1	25
Urban	2	50	3	75
Total	4	100	4	100

Figure 9: Bar diagram showing the distribution based on region of stay

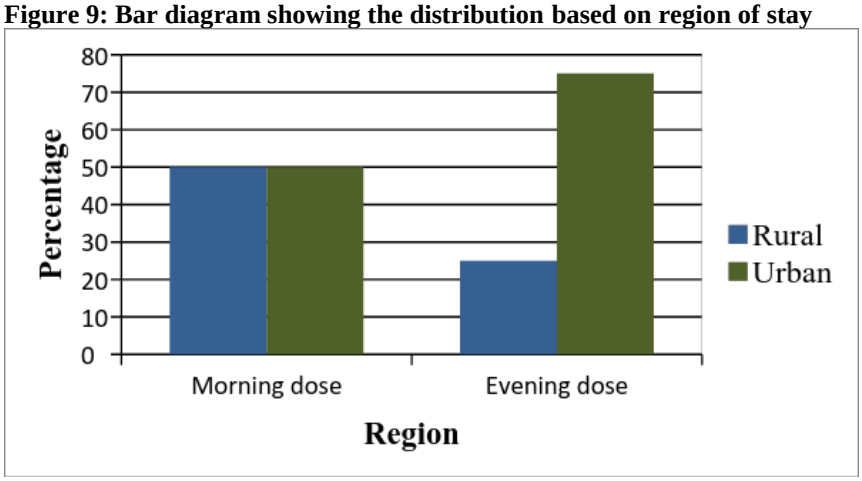
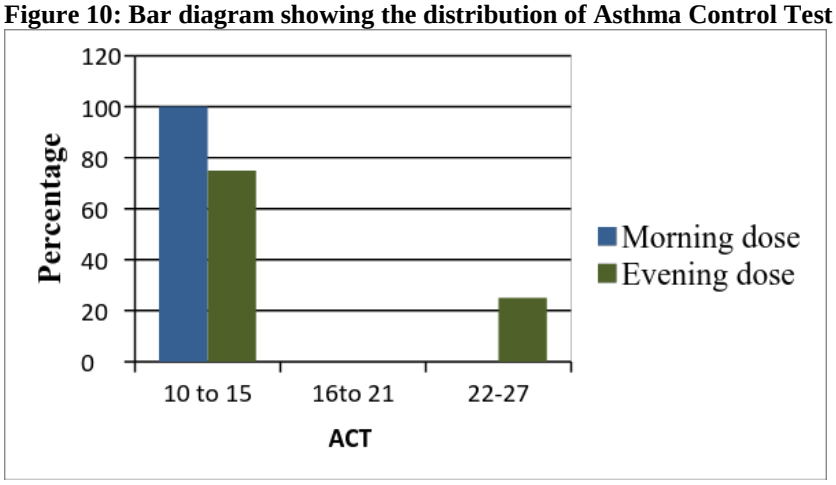


Table 10: Distribution of Asthma Control Test (ACT) values

ACT Values	Morning Dose		Evening Dose	
	Number	Percentage (%)	Number	Percentage (%)
10 to 15	4	100	3	75
16to 21	0	0	0	0
22-27	0	0	1	25
total	4		4	

Figure 10: Bar diagram showing the distribution of Asthma Control Test (ACT) values



SPIROMERTY DATA

Table 11: Comparison of Forced Expiratory Volume per second (FEV1) between morning and evening dosing

Variables	Morning Dose		Evening Dose	
	Mean	Std. Dev	Mean	Std. Dev
**** BASELINE***				
FEV1	**1.125**	**0.367**	**1.528**	**0.284**
**** FOLLOW UP***				
FEV1	**1.35**	**0.24**	**1.843**	**0.356**

Figure 11: Bar diagram showing the Comparison of Forced Expiratory Volume per 1 second (FEV1) between morning and evening dosing

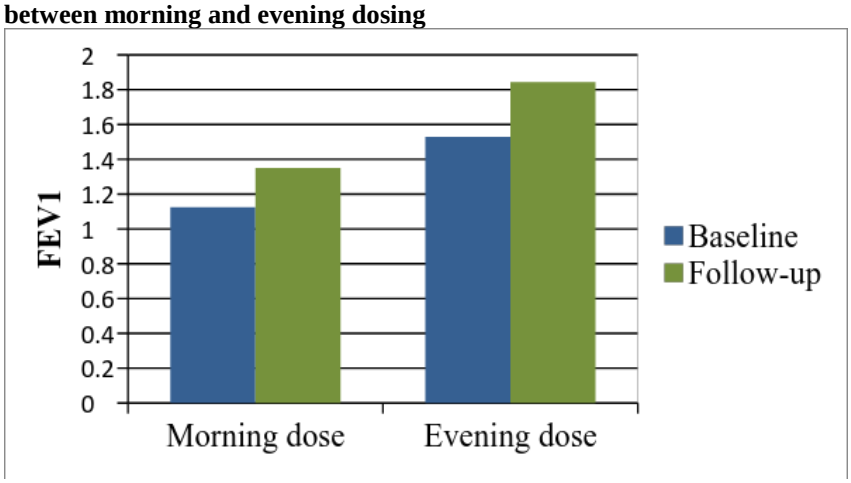


Table 12: Comparison of Forced Vital Capacity (FVC) between morning and evening dosing

Variables	Morning Dose		Evening Dose	
	Mean	Std. Dev	Mean	Std. Dev
**** BASELINE***				
FCV	**1.6025**	**0.568**	**2.495**	**0.25**
**** FOLLOW UP***				
FCV	**1.85**	**0.639**	**1.76**	**0.76**

Figure 12: Bar diagram showing the comparison of Forced Vital Capacity (FVC) between morning and evening dosing

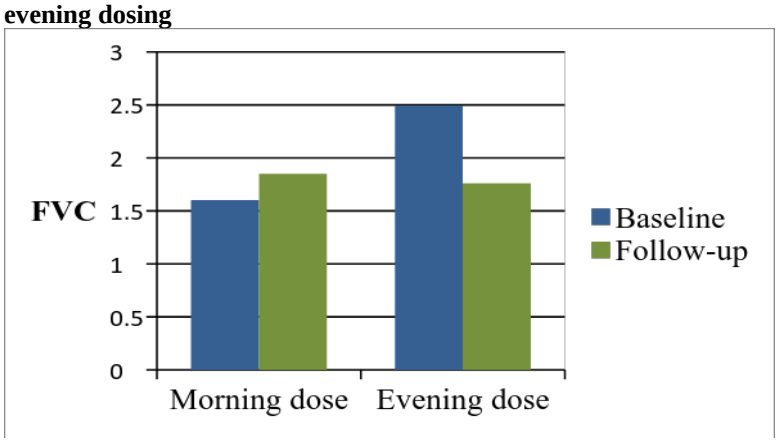
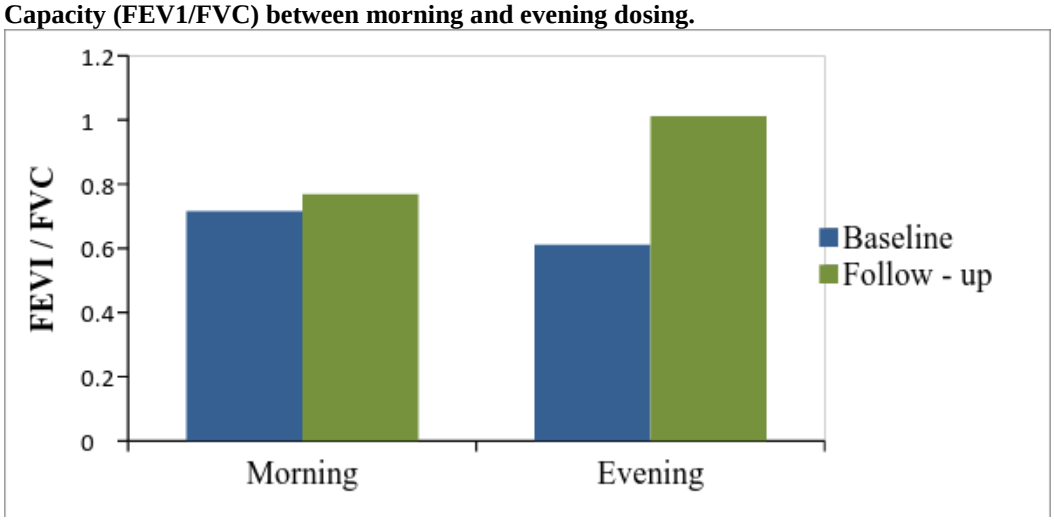


Table No 13: Bar diagram showing the comparison of Forced Expiratory Volume per second/ Forced Vital Capacity (FEV1/FVC) between morning and evening dosing.

FEV1/FVC	Morning dose		Evening dose	
	BASELINE	FOLLOW UP	BASELINE	FOLLOWUP
MEAN	0.715	0.769	0.612	1.01
Standard deviation	0.105	0.178	0.091	0.420

Figure 13: Bar diagram showing the comparison of Forced Expiratory Volume per second/ Forced Vital Capacity (FEV1/FVC) between morning and evening dosing.



DISCUSSION

Asthma is a chronic inflammatory disease of the respiratory tract. It is characterized by the hyper-responsiveness of the lower airways to several stimuli. Symptoms experienced by patients include difficulty in breathing, bronchospasm and excessive secretion of mucus[13]. The aim of asthma management is to achieve and maintain asthma control by treating inflammation and relieving broncho-constriction and symptoms[14]. The prospective study entitled "a study to evaluate the effect of time of dosing of a bronchodilator Deriphyllin in asthma patients**"** was conducted at KIMS Hospital and research centre, Bengaluru. After obtaining the ethical clearance, 8 patients who fulfilled the inclusion and exclusion criteria were enrolled for the study, after obtaining a written consent from them to participate in the study. To compare the effect of morning dosing versus evening dosing of Deriphyllin, which has been reported to exhibit circadian variation, the patients were divided into two groups(n=4 in each group) alternatively. Asthma Control Test questionnaire was also administered for each group (n=4).

DEMOGRAPHIC DETAILS

A total of 8 mild persistent asthma patients were enrolled in this study. They were divided into 2 groups, group A consisted of patients who were on morning dosing and group B of patients on evening dosing of Deriphyllin. Among the total of 8 patients, 2 were females and 6 were males. As illustrated in Table No- 2, male patients were more in number in both the groups.

Age wise distribution: Table No-3 indicates the age wise distribution of patients. In Group A, it was observed that 50% of the patient population was in the age group of 25-31 years and 25% were between 18-24 years and 53-59 years. In Group B, it was observed that 25% were 18-24 years, 25-31 years, 46-52 years &53-59 years. Mean age±standard deviation in group A was found to be 34±15.07 years and in group B 37.5±15.107 years. It was observed that maximum of mild persistent asthma patients were between 25-31 years.

Distribution based on weight: Observations in Table No -4 showed that 50% of the patient population was in the weight group of 40-54 kgs (group A). In Group B, 50% were 40-54 kgs. Mean weight in group A was found to be 64.25±18.966 kgs and in group B it was found to be 54.5±18.966 kgs. It was observed that overall mean height was between 40-54 kgs.

Distribution based on height: Mean height in group A was found to be 165.5±9.258cms and in group B it was found to be164.5±9.258 cms (Table no-5). It was observed that 50% each of mild persistent asthma patients were between155-159cms and 170-174cms.

Distribution based on occupation: Table No-6 shows the distribution level of occupation on both the groups of the study. In Group A, it was observed that 75% of the patient population were employed, 25% were students. Group B comprised of students and housewives (25% each). The incidence of mild to persistent asthma was found to be more in the patients who were employed rather than housewives.

Educational status: In Group A, 3 (75%) patients were educated up to SSLC and 1 (25%) patient completed graduation or degree (Table No: 7). In Group B, it was observed that 2 (50%) were educated up to PUC and other 2 (50%) patients were illiterate.

Family history of asthma: In Group A, it was observed that 75% of the patient population did not report any family history of asthma. 50% of patient population had family history and others did not have any family history in group B (Table No 8). It was also observed that majority of mild persistent asthma patients were not having family history of asthma.

Distribution based on region of stay: The present study comprised of patients both from rural and urban region. In Group A, 50% of the patient population was from rural and urban region (50%). In Group B, 75% were from urban and 25% from rural region. During this study from (Table No -9), it was seen that patients from urban region were prone to asthma in comparison to rural region.

Asthma Control Test Questionnaire (ACT): Table No-10 indicates ACT Value distribution of patients in morning and evening dose in two groups during baseline. In Group A, it was observed that the ACT values of 4 patients were in the range of 10-15 at baseline. In Group B, it was observed that the ACT values of 3 patients were in the range of 10-15 and 1 patient in the range of 22-27.

ANALYSIS OF EFFICACY: SPIROMETRY RESULTS

Forced Expiratory Volume per Second (FEV1)

Table No-11 indicates the Forced Expiratory volume per second (FEV1) recording following morning and evening dose at baseline and follow-up. Mean FEV1 was found to be 1.125±0.37 (baseline) and 1.35±0.24 (follow up) after the administration of morning dose of Deriphyllin retard. Mean FEV1 was found to be 1.528±0.28 (baseline) and 1.843±0.36 (follow up) after the administration of evening dose of Deriphyllin retard.

Forced Vital Capacity (FVC)

Table No-12 indicates the Forced Vital Capacity (FVC) recording following morning and evening dose at baseline and follow-up. Mean FVC was found to be 1.6025±0.57 (baseline) and 1.85±0.64 (follow up) after the administration of morning dose of Deriphyllin retard. Mean FVC was found to be 2.495±0.25 (baseline) and 1.76±0.76 (follow up) after the administration of evening dose of Deriphyllin retard.

Forced Expiratory Volume per second/ Forced Vital Capacity (FEV1/FVC)

Table No: 13 indicate the ratio of Forced Expiratory Volume per second /Forced Vital Capacity (FEV1/FVC) recording following morning and evening dose at baseline and follow-up. Mean FEV1/FVC was found to be 0.72±0.11 (baseline) and 0.769±0.178 (follow up) after the administration of morning dose of Deriphyllin retard. Mean FEV1/FVC was found to be

0.612±0.091 (baseline) and 1.01±0.42 (follow up) after the administration of evening dose of Deriphyllin retard.

CONCLUSION

In conclusion, the spirometry results reveal that in our study population evening dose of Deriphyllin Retard in mild to persistent asthma patients was efficacious to a higher extent than the morning dosing. This is very beneficial as the increase in the severity of airway obstruction during the early morning hours is the common occurrence in bronchial asthma. The morning dipping in asthma which is associated within exaggerated circadian variation in pulmonary function could be prevented with the evening dose of Deriphyllin Retard.

LIMITATIONS OF THE PRESENT STUDY

1. Sample size with large patient population would have revealed better results.
2. Daily peak flow meter studies were not done due to logistics and cost.
3. Study was conducted for 3months from March to May, during which attacks were less.
4. Pharmacoeconomic analysis; direct and indirect costs analysis were not done as all the patients could not recollect the costs incurred.
5. Pharmacokinetic studies for the plasma concentration of etophylline and theophylline used in the study were not done, as it would be expensive and burden on the patients.

RECOMMENDATIONS FOR FURTHER STUDY

1. Long term studies can be collected to meet all the seasons.
2. Multi Centre studies can be conducted to get better results.
3. A similar study with larger population can be conducted for significant results.
4. Therapeutic Drug Monitoring of Etophylline and Theophylline, as Theophylline is having narrow therapeutic index.

CONFLICT OF INTEREST

There is no conflict of interest associated with the authors of this paper.

ACKNOWLEDGEMENTS

Authors are thankful to Dr Halappa Chalageri, Sr DMO/ Physician, SW Railway, Ministry of Railways, Govt of India, Bangalore for his support in providing Spirometer and Dr Geetha Kishore, Dr Meera NK, Mr Kiran Nagaraju and Mr Shekar HS, Faculty members of Dept of Pharmacy Practice for their co-operation in the study.

REFERENCES

1. Global strategy for asthma management and prevention updated 2012, Global Initiative for Asthma (GINA). Revised asthma guidelines 2012. Access Online: http://www.ginasthma.org. Accessed on 4 th Jan, 2014.
2. Alilgne CA, Auinger P, Byard RS. 'Risk factors for Asthma.' American Thoracic Society. Maryland. 2000 April; 72(3): 873-77.
3. Surendra Adusumalli, Patan Fayaz, Nagaraju B, Puranik DS, Purohit Shanthraj. Antiasthmatic activity of aqueous extract of pistacia integerrima galls. Wudpecker Journal of Pharmacy and Pharmacology 2013. Wudpecker Journals; 2013 May: Vol. 2(3), pp. 026-032.
4. Sathya prabha TN. Murthy H. 'Asthma issues and trends'. International journal of pharmacology.Dublin. 2001 Jan; 23(5): 80-6.
5. Jindal SK. Asthma control in the first decade of 21 century. Indian J Med Res 2007; 125:604-7.
6. Aggarwal AN, Chaudhry K, Chhabra SK, D'Souza GA, Gupta D, Jindal SK, *et al.,* Prevalence and risk factors for bronchial asthma in Indian adults: A multicentre study. Indian J Chest Dis Allied Sci 2006; 48:13-22**.**
7. Neal JS. Morgan MS. 'Relationship among Household dust and Allergic asthma' American journal of Asthma immunology. Ohio. 2002 April; 88(4): 410-15.
8. Rai SP, Patil AP, Vardhan V, Marwah V, Pethe M, Pandey IM. Best treatment Guidelines for Bronchial Asthma. MJAFI 2007; 63:264-8.
9. Vikas Seth. Classification of Drugs with Drugs of Choice. Aditya Medical (publishers), 3rd ed. 2009;p.no:44.
10. Undem BJ. Pharmacotherapy of Asthma. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman and Gillman's The Pharmacological Basis of Therapeutics. 11th ed.Mc graw hill: New York; 2001. P.717-36.
11. Barnes PJ, Pauwels RA. Theophylline in the management of Asthma: Time for appraisal? Eur Respir J. 1994; 7: 579-91.
12. Devang NW, Hemant TD. Ultra performance liquid chromatography (UPLC) method development and validation for the simultaneous estimation of etophylline and theophylline in pharmaceutical dosage form. International journal of life science & pharma research. 2012 July-September; 2(3):19.
13. Seshni Sewlall. Design of a triple layer double disk tablet configuration for phase controlled drug delivery. 2009; 7-9.
14. Hanxiang nie, Guqinzhang, Minliu, Xuhong ding, Yi huang, Suping hu. Efficacy of theophylline plus salmeterol/ fluticasone propionate combination therapy in patients with asthma, respiratory medicine. 2013; 107:347-354.