Int J Pharm Bio Sci 2014 April ; 5 (2) : (P) 214 - 222

Research Article **Pharmacology**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

THEOPHYLLINE AND ACEBROPHYLLINE IN MILD BRONCHIAL ASTHMA: A COMPARATIVE STUDY OF EFFICACY AND SAFETY

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ABSTRACT

To compare the efficacy and tolerability of Theophylline and Acebrophylline in mild persistent asthma.A randomized, open, parallel clinical study was conducted on 100 patients of mild persistent asthma. After baseline assessments, Theophylline was prescribed to 50 patients and Acebrophylline to another 50 for 4 weeks. The efficacy variables were change in asthma symptom scoring and pulmonary function test. At follow-up, the patients were re-evaluated and analyzed by statistical tools.The mean peak expiratory flow rate before and after therapy in Theophylline group was 202.6±41.6 and 222±45.1 ml respectively and in Acebrophylline group 183.3±40.8 and 237.3±47.5 ml respectively. The mean FEV1 before and after therapy in Theophylline group was 1.73±0.75 and 1.88±0 ml respectively and in Acebrophylline group 1.65±0.73 and 2.26±0.73 ml respectively. PEFR and FEV1, Cough scoring and sputum quantity was improved significantly in Acebrophylline group than Theophylline group. Side effects were significantly low in Acebrophylline than Theophylline group. Acebrophylline was found to be superior to Theophylline in terms of efficacy and tolerability in patients with mild bronchial asthma as evidenced by subjective and objective means.Acebrophylline was found to be superior compared to Theophylline in mild persistent asthma.

KEY WORDS:Bronchial asthma, Forced expiratory volume (FEV), Peak expiratory flow meter(PEFM), Theophylline, Acebrophylline

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INTRODUCTION

Asthma is a complex syndrome that involves potentially permanent airway obstruction, airway hyperresponsiveness, and multicellular inflammation. It is characterized by dyspnea, wheezing, cough, chest tightness, airway hyper-responsiveness and variable airflow obstruction. The clinical diagnosis of asthma can be corroborated by suggestive changes in pulmonary function tests. When patients complain of symptoms more than once weekly but less than once daily with normal or near normal lung function, it is called mild persistent asthma[1]. In some patients, narrowing of the airways may be part of an allergic reaction, triggering the release of biologically active mediators. In other patients, specific stimuli trigger episodes and suggest an etiologic relationship (exercise, airway cooling, or stress).In majority of patients, the cause of the airway hyperreactivity is unknown. Specific cause that have been proposed include imbalance within the nervous system, deficiency of beta receptors, excess contraction of airway smooth muscle, imbalances in mediator production, and immune regulatory defects[2].Hypersecretion is a significant symptom in bronchial asthma, particularly following bronchospastic crisis. The prevalence of asthma has increased in most countries since the 1970s. About 300 million people worldwide have asthma and by 2025 it has been estimated that a further 100 million will be affected[3]. There is a noticeable increase in health care burden from asthma in several areas of the world. There is also a global concern on the change in asthma epidemiology and clinical spectrum[4]. The aims of pharmacological management of asthma are the control of symptoms, including nocturnal symptoms and exercise-induced asthma, prevention of exacerbations and the achievement of best possible pulmonary function, with minimal side effects[3].

As per GINA guidelines, step 2 approach is used in mild persistent asthma[5]. In step 2 approaches, low dose corticosteroid inhalation or alternately leukoterine modifier, theophylline is used[6]. It provides bronchodilatation in asthmatics, anti-inflammatory properties, enhance mucociliary clearance, and strengthen diaphragmatic contractility. Theophylline serum concentrations need to be monitored closely owing to the drug's narrow toxic therapeutic range[7]. Theophylline has been shown to inhibit phosphodiesterase (PDE) which degrades cyclic nucleotides intracellularly. The concentration of cyclic nucleotides is increased. Broncho dilatation, cardiac stimulation and vasodilatation occur when cAMP level rises in the concerned cells. Several isoenzymes of the PDE superfamily exist in different tissues. Theophylline is a subtype nonselective PDE inhibitor, But PDE4 and PDE5 inhibition is mainly responsible for bronchodilatation[8]. Though theophylline has been the mainstay in xanthine therapy for several decades and proven to be a dependable bronchodilator it is plagued by several extrapulmonary effects including nausea, GI upset, cardiac and CNS stimulation at serum concentration that cross the therapeutic window[9,10]. Acebrophylline is a newer bronchodilator in xanthine group[11]. Hence the present study is undertaken to assess the efficacy of acebrophylline compared to theopyllinein patients with bronchial asthma.

MATERIALS AND METHODS

Patients

The study was conducted on 100 patients of mild persistent asthma attending the outdoor department of Pulmonology of our institute.The study population included patients irrespective of sex, aged between 18 and 50 years suffering from mild persistent asthma with forced expiratory volume in 1 second (FEV1) of 80% or more of the predicted value before administration of a bronchodilator; and they were started on 2.5 mg salbutamol neubalizer at 20 minutes interval and the difference in the improvement before and after inhalation was recorded by using peak expiratory flow meter and spirometer. Those who showed improvement in PEFR more than 15% or FEV1 more than 12% or FEV1> 200 ml were selected

for study. Patients with severe asthma, endocrine disorder, diabetes, hypothyroidism, chronic renal failure, neuropsychiatric illness, cardiac disease, hypertension, pulmonary hypertension, thoracic abnormalities were excluded. Pregnant and lactating mothers were also not included. Patients > 40 yrs who have associated systemic illness were also excluded from the study.

Study Design

The study was an open label, single centre randomized comparative trial conducted between August 2004 and March 2006 following the approval from the institutional ethical committee. A written informed consent was obtained from all the patients who participated in the study after explaining the patient's diagnosis, the nature and purpose of a proposed treatment, the risks and benefits of the proposed treatment (acebrophylline/theophylline), alternative treatment and the risks and benefits of the alternative treatment. After randomization, the patients were divided into two treatment groups. A total of 50 patients were allocated in the acebrophylline group who received acebrophylline100 mg twice daily and another 50 patients in the theophylline group who received theophylline 100 mg twice daily for 4 weeks. Each patient was advised to return the used blister packs at visit 1 in order to maintain accountability of study medication. They were assured not to take any supportive or concomitant medication. Patients were given a card carrying details of adverse effects in vernacular language as shown below and motivated them to mark the side effects, experienced during drug therapy on a meticulous manner. Patient was advised to regular follow-up for every week (Visit 0 - First day, visit 1 - End of the first week, visit 2 - End of second week, visit 3 - End of third week, visit 4 - End of fourth week). At the visit 0, after detailed history on baseline symptomatology, clinical evaluation [cough scoring and sputum quantity] and pulmonary function test [FEV 1, PEFR] were done. Patients' prognosis was assessed with cough scoring and sputum quantity in every week. After 4 weeks, pulmonary function test was repeated and clinical improvement was assessed in terms of change in FEV 1, PEFR and asthma symptom [cough scoring and sputum quantity].

Efficacy and safety variables

The efficacy variables were change in the severity of asthma symptom score and pulmonary function test from baseline to every week. Asthma symptom scoring has been considered as the primary outcome of this study and Pulmonary function test as the secondary outcome. Cough intensity, quantity of sputum were evaluated at the end of 1st week, 2nd week, 3rd week and 4th week. The cough symptom severity was defined as follows:0 -not present, 1–mild, 2–moderate, 3–severe. At the same intervals, the quantity of sputum (ml/24hrs) was also assessed. Hypersecretion is a significant symptom in bronchial asthma, particularly following bronchospastic crisis. A pulmonary function test was done by a Helios 401 spirometer followed by computerized analysis. FEV1 (forced expiratory volume in 1 second) and PEFR (peak expiratory flow rate) were assessed at baseline and 4th week of treatment.Tolerability was assessed in terms of reported adverse experiences and vital signs, which were measured at baseline and at the end of the study.

Statistical analysis

Data were analysed statistically using Students T test.$P<$ 0.05 was considered statistically significant. The statistician was blinded to the groups during analysis.

RESULTS

Efficacy Analysis

Both Intensity of cough and Sputum quantity are reduced significantly in Acebrophylline group than Theophylline group in ($p<0.001$) and ($p<0.001$)[Table-1&Graph-1]

Table 1a
Intensity of cough before and after treatment with theophylline and acebrophylline

Basic characteristic	Theophylline	Acebrophylline
	Mean± S.D	Mean± S.D
Base line	2.10 ± 0.712	2.233 ± 0.679
1st week	1.967 ± 0.669	1.867 ± 0.629
2nd week	1.767 ± 0.636	1.767 ± 0.568
3rd week	1.567 ± 0.504	1.300 ± 0.596
4th week	1.433 ± 0.504	0.633 ± 0.490

0= not present, 1=mild, 2-moderate, 3=severe (p<.001 highly significant)

Graph1a
Intensity of cough before and after treatment with theophylline and acebrophylline

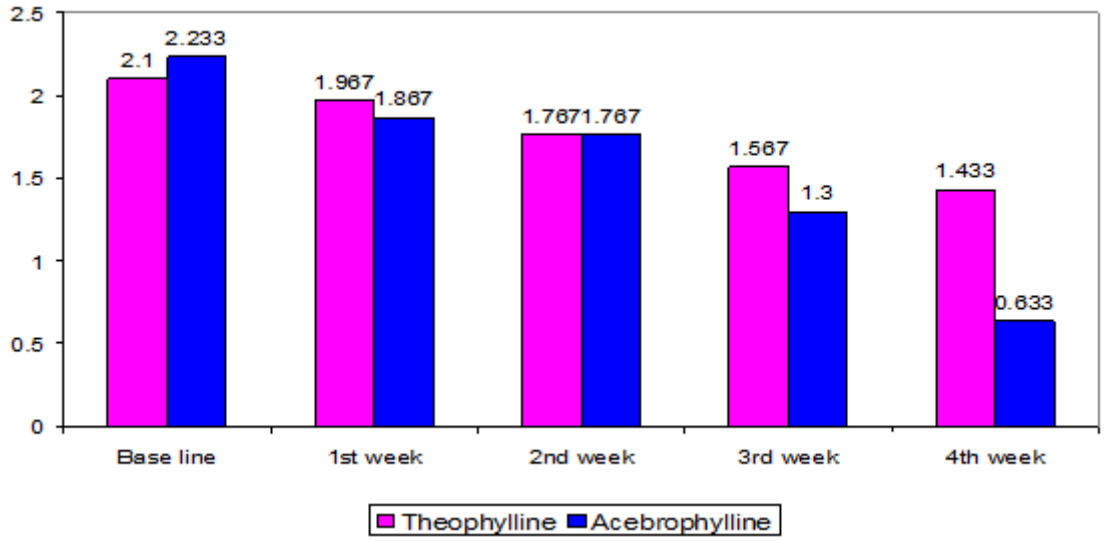


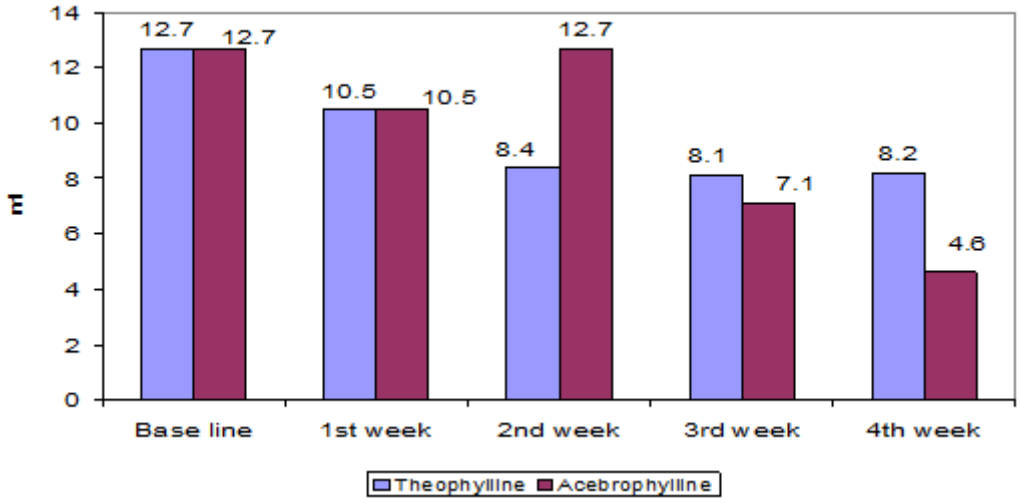
Table 1b
Sputum quantity before and after treatment with theophylline and acebrophylline

Basic characteristic	Theophylline	Acebrophylline
	Mean ± S.D	Mean± S.D
Base line	12.700 ± 2.961	12.700 ± 2.961
1st week	10.467 ± 1.717	10.467 ± 1.717
2nd week	8.367 ± 1.671	12.700 ± 2.961
3rd week	8.133 ± 1.479	7.133 ± 2.255
4th week	8.167 ± 1.147	4.567 ± 1.194

(p < 0.001 Significant)

Graph 1b

Sputum quantity before and after treatment with theophylline and acebrophylline



The mean FEV1 before and after therapy in Theophylline group was 1.73 ± 0.75 and 1.88 ± 0.80 respectively and the mean in Acebrophylline group was 1.65 ± 0.73 and 2.26 ± 0.73 respectively. Pulmonary function (FEV1) improved significantly after oral exposure to drugs irrespective of the type (Table-2&Graph-2).

Table 2

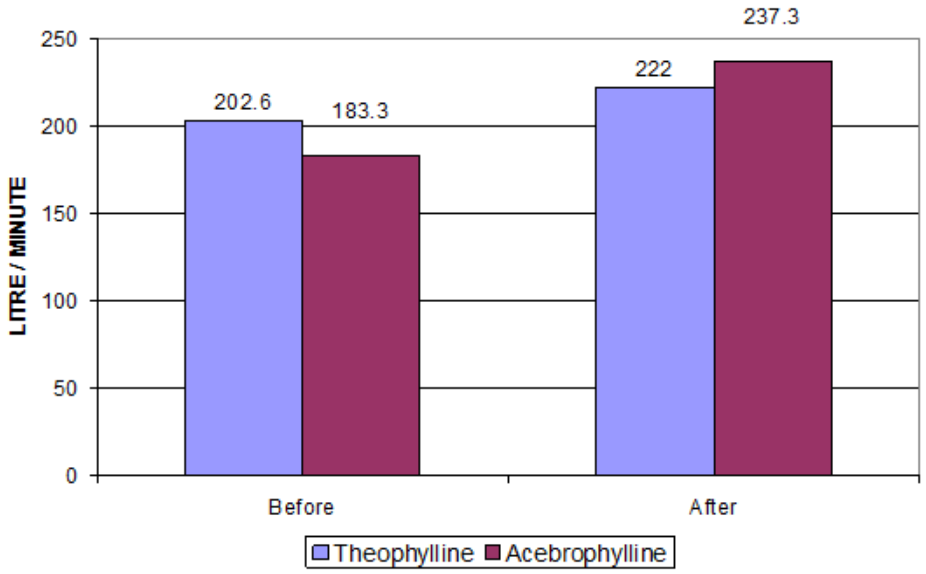
FEV1 comparison among theophylline and acebrophylline

Basic characteristic	Theophylline		Acebrophylline	
	Before	After	Before	After
Mean ± SD	1.73±0.75	1.88±0.80	1.65±0.73	2.26±0.73

(p < .01 -significant)

Graph 2

FEV1 comparison among theophylline and acebrophylline



However the improvement was very high in the Acebrophylline group (p<0.01) thus indicating that Acebrophylline has better effect as bronchodilator. The mean PEFR before and after therapy in Theophylline group was 202.6 ± 41.6 and 222 ± 45 respectively and the mean in Acebrophylline group was 183.3 ± 40.8 and 237.3 ± 47.5 respectively (***p<.001).

Table 3

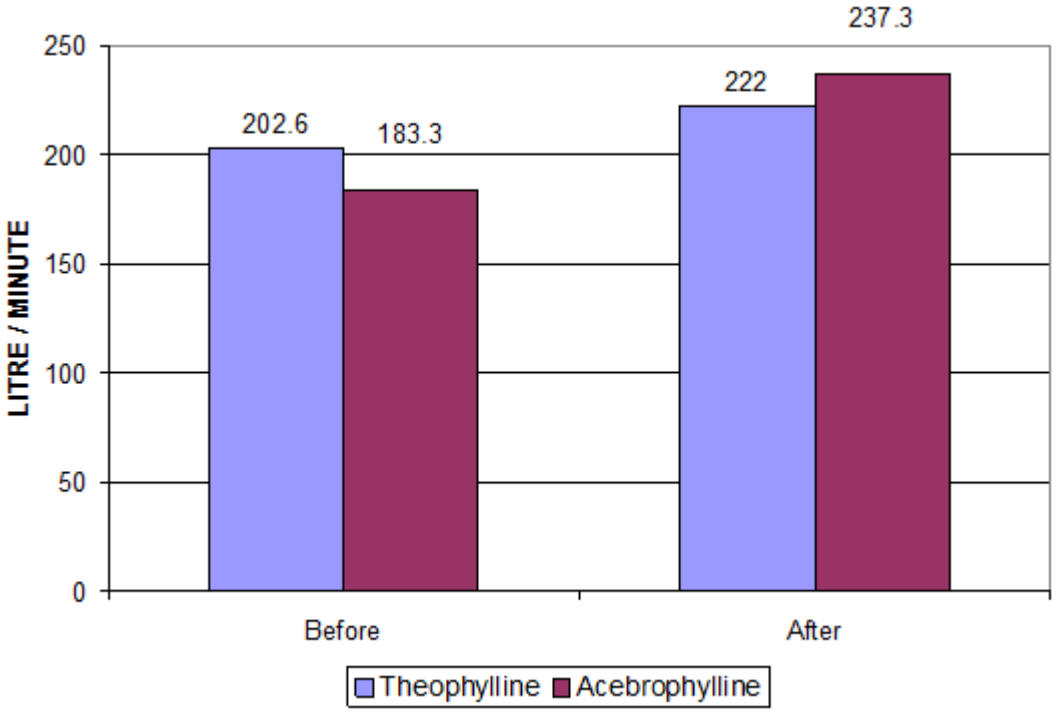
Peak expiratory flow rate comparison among theophylline and acebrophylline

	Theophylline		Acebrophylline	
Basic characteristic	Before	After	Before	After
Mean± S.D	202.6 ±41.6	222±45.1	183.3±40.8	237.3±47.5

(p < .001 – Highly significant)

Graph 3

Peak expiratory flow rate comparison among theophylline and acebrophylline



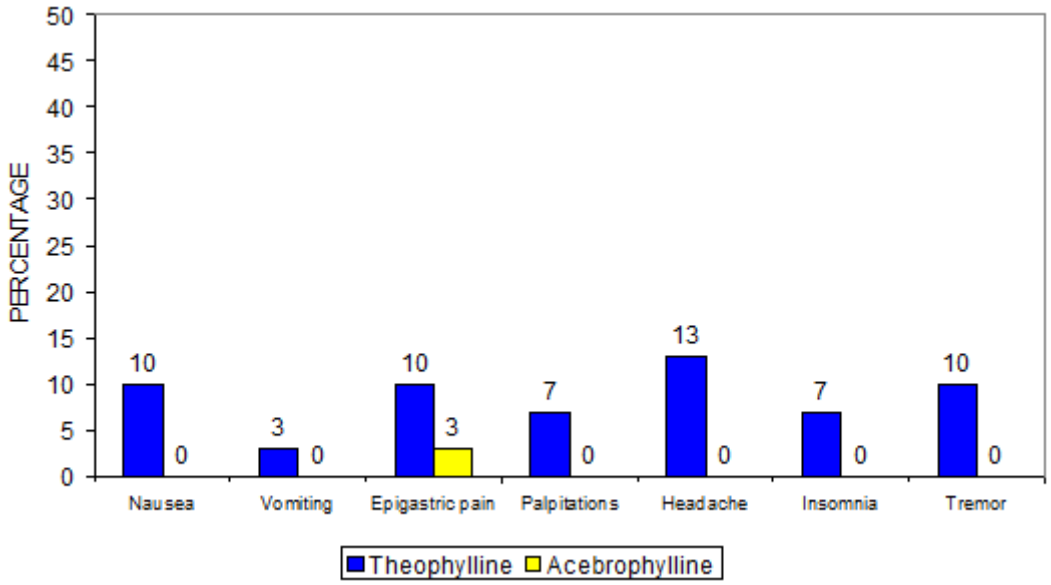
The PEFR improvement was very high in the Acebrophylline group (p<0.001) thus indicating that Acebrophylline has better effect as bronchodilator. (Table-3&Graph-3)

In the Theophylline group, out of 50 patients who experienced adverse effects, 13% complained of headache, 23% had nausea/vomiting/epigastric pain, 2% patient complained of insomnia, 10% patients complained of muscular tremor and other 7% had experienced palpitation. In the Acebrophylline group, 3% patient only had epigastric pain. Side effects were significantly less with Acebrophylline group. (Table-4&Graph-4)

Table 4
Nature of side effects

SL.NO.	SIDE EFFECTS	THEOPHYLLINE	ACEBROPHYLLINE
1.	**GIT EFFECTS**		
	Nausea	**3(10%)**	**0**
	Vomiting	**1(3%)**	**0**
	Epigastric pain	**3(10%)**	**1(3%)**
2.	**CVS EFFECTS**		
	Palpitations	**2(7%)**	**0**
3.	**CNS EFFECTS**		
	Headache	**4(13%)**	**0**
	Insomnia	**2(7%)**	**0**
	Tremor	**3(10%)**	**0**

Graph 4
Nature of side effects



DISCUSSION

Bronchial asthma is known for time immemorial. Variety of therapeutic agents, though available in different systems of medicine, modern scientific medicines try to act at the cellular level to extent with constraints. Traditionally, Theophylline, a nonspecific phosphodiesterase (PDE) inhibitor, has been used as a bronchodilator. Recently, it has become apparent that a number of inflammatory cells specifically possess the PDE isoenzyme IV, raising the possibility that modulation of this enzyme may lead to anti-inflammatory effects. Acebrophylline inhibits phospholipase A, and phosphatidylcholine leading to lesser production of the powerful pro-inflammatory substances like leukotrienes and tumour necrosis factor[12]. By inhibiting the synthesis and release of these inflammatory mediators, Acebrophylline reduces inflammation, a key factor in airway obstruction, especially in chronic forms. Acebrophylline acts as MUCOREGULATOR and restore the normal viscosity of abnormal bronchial secretions & improves mucociliary transport. It increases the synthesis of PULMONARY SURFACTANT and facilitates

non-ciliary mucus clearance. It's ANTI INFLAMMATORY / ANTI REACTIVE ACTIVITY reduces bronchial airway hyperresponsiveness and reduces the production of Leukotriene B4&TNF. Its BRONCHODILATOR effect significantly improves lung function & improves partial pressure of oxygen[13]. From the present study it is clear that Acebrophylline has distinct advantage for those patients suffering from bronchial asthma. The observations were supported with available literature since the cellular, experimental and clinical properties of Acebrophylline are superior to Theophylline. G.Beulcke et al, Department of Respiratory Pathophysiology, Pneumology, Italy showed that results are in agreement with the bronchodilator effect of Theophylline and with bronchodilator and mucoregulating effect of Acebrophylline. Safety was considered very well in both groups[14]. H.Weber, MD et al, Munchen, FDR showed cough intensity and sputum quantity was improved significantly in Acebrophylline group than Theophylline[15]. The present study is comparable with study of G.Beulcke et al, Italy and H.Weber, MD et al, Munchen, FDR. Hence, it is suggested that Acebrophylline may be used in day to day clinical practice for the patients who are in need of the same.

CONCLUSION

Highly significant improvement in PEFR & FEV1 was noticed in Acebrophylline group. Cough Intensity and Sputum quantity was reduced in Acebrophylline group than Theophylline. All parameters improved remarkably in Acebrophylline group than Theophylline group. Side effects were more among Theophylline than Acebrophylline. In conclusion, from the results of the present comparative clinical study of Theophylline and Acebrophylline, Acebrophylline would be a better choice in mild persistent asthma compared with Theophylline owing to its better efficacy and safety profile.

ACKNOWLEDGEMENT

The authors gratefully acknowledge Dr.Parameswari, Director and Head of the Institute of pharmacology, Dr.Navajothi Assistant Professor of pharmacology, Dr.C.Ramesh, Head of the Department of Thoracic Medicine, Government Rajaji hospital, Madurai, for their support and guidance for the successful completion of this study.

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