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# **Original Research Article**

# A comparative study of efficacy and tolerability of doxofylline over other methylxanthenes in mild to moderate persistent bronchial asthma patients in a tertiary care hospital

Satyendra K. Alladi\*, Imran Khan

Department of Pharmacology, Kakatiya Medical College, Warangal, Telangana, India

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# \*Correspondence to: Dr. Satyendra K. Alladi,

Email: askvijpaniram99@ gmail.com

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work is properly cited.

## **ABSTRACT**

Background: Studies have shown that doxofylline is endowed with a remarkable bronchodilator activity with less extra respiratory effects than other methylxanthines. To compare the efficacy and tolerability of doxofylline over other methylxanthines in mild to moderate persistent bronchial Asthma patients. Methods: It is a comparative study conducted in patients of mild to moderate persistent bronchial Asthma in the outpatient department of regional chest hospital. The subjects were randomly assigned into 2 groups, one group treated with oral doxofylline and the other with theophylline oral or Deriphylline. Efficacy was measured objectively using spirometric parameters like FEV1 (Forced Expiratory Volume at the end of 1 second), FVC (Forced Vital Capacity), FEV1/FVC and PEFR (Peak Expiratory flow Rate), Subjectively by the Asthma control test questionnaire, subjective rating of Asthma control and the need for use of rescue medications like β2 agonists in the previous four weeks. Tolerability were done at base line and at the end of study.

**Results:** Doxofylline compared to other methylxanthines groups was statistically better with respect to subjective parameters like Asthma control tests questionnaire, subjective rating of Asthma control. Doxofylline had equal efficacy with spirometric parameters compared to other methylxanthines. Doxofylline was significantly better tolerated with adverse drug reactions noted in 10% compared to 28% in other methylxanthins group.

**Conclusions:** Doxofylline with better tolerability profile and equivalent efficacy seemed to be a good alternative to other methylxanthines in the treatment of bronchial Asthma.

**Keywords:** Bronchial asthma, Doxofylline, Efficacy, Methylxanthines, Tolerability

# INTRODUCTION

Bronchial asthma is a chronic inflammatory disorder characterized by airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing particularly at the night or early morning. Often associated with variable, widespread obstruction that is reversible either spontaneously or with treatment.<sup>1,2</sup>

Asthma is prevalent worldwide affecting more than 300 million.<sup>3</sup> Global prevalence ranges from 1 to 18%.<sup>1</sup> India has approximately 15-20 million asthmatics.

Asthma management is to achieve and maintain clinical control. Effective control of acute attacks; and in the long term, prevention of further episodes and airway remodelling at an early stage. Medications to treat asthma classified as controllers and relievers. Controllers, taken daily for clinical control of asthma by its anti inflammatory

effects. They include inhaled and systemic corticosteroids, theophylline. Cromones and anti-Ig E. Relievers, medications used as needed basis, to reverse bronchoconstriction and relieve symptoms. They include rapid acting inhaled  $\beta_2$  agonists, inhaled anticholinergics, short acting theophylline, and short acting oral  $\beta_2$  agonists.  $^{1,2}$ 

Methylxanthines constitute non-selective phosphodiesterase inhibitors. Characterized by mild bronchodilator, immunomodulator, anti-inflammatory, bronchoprotective, mucoregulatory, inflammatory cell stabilizing and steroid sparing properties.<sup>3,4</sup>

Theophylline, a methylxanthine with narrow therapeutic index, often results in wide range of adverse effect of cardiac, gastro - intestinal and central nervous systems accounting for the poor compliance and high dropout rates. Doxofylline [7-(1,3-dioxolane-2-methyl1) theophylline] has equal or superior bronchodilator activity than theophylline and better safety profile due to reduced affinity for adenosine  $A_1$  and  $A_2$  receptors. It ameliorates spirometric parameters, reduces attack rates and the need for  $\beta 2$  agonists.<sup>4</sup>

Pharmacotherapy forms a major role in both treatment and control of asthma. Hence, there is constant search for new drugs with better efficacy and reduced side effect profile. Cochrane's group concludes xanthines as first choice therapy to prevent and relieve symptoms in asthma and to reduce the requirements of rescue medication in mild to moderate asthma.<sup>4</sup> Present study is aimed to compare the efficacy and tolerability of doxofylline over other methylxanthines in mild to moderate persistent bronchial asthma patients.

#### **METHODS**

It was a single center, prospective comparative study, period of study was from January 2015 to September 2015.

## Study population

Patients with mild to moderate persistent bronchial asthma attending outpatient department of chest hospital, study was started after the protocol was approved by the Institutional Ethics Committee. All the patients diagnosed with mild to moderate persistent Bronchial Asthma were screened and selected based on following criteria.

# Inclusion criteria

- Patients giving informed consent
- Patients aged between 18-65 years of either sex.
- Patients clinically diagnosed with mild to moderate persistent bronchial asthma.
- Patients with FEV1 (Forced expiratory volume in the first second of expiration)
- Value of 50% or more of predicted.

- Improvement in FEV1 greater than 12% after bronchodilator inhalation.
- Patients on inhaled corticosteroids.

#### Exclusion criteria

Major respiratory illness other than asthma like Chronic obstructive pulmonary disease or other relevant lung disease causing alternative impairment in lung function.

- Patients with co-morbid conditions Ischemic heart disease, congestive cardiac failure, renal and hepatic dysfunction, neurological, other endocrinal and hematological abnormalities.
- Patients unwilling to comply with the requirement of the protocol.
- Smokers, pregnant, and lactating women.
- History of known allergy/intolerance/hyper sensitivity to study drugs.
- Patients on regular treatment with drugs that interact with methylxanthines.
- Patients on systemic corticosteroids.
- Patients with Class III obesity according to Indian guidelines for obesity.

The study subjects giving informed consent, fulfilling the inclusion/exclusion criteria were assigned into 2 groups of 30 patients each.

- *Group 1:* Patients treated with doxofylline 400mg once a day.
- Group 2: Patients treated with other methylxanthines like Theophylline 200mg SR once a day Deriphylline 150mg SR two times a day.

Assessment was done by measuring the efficacy parameters like pulmonary Function Test (Spirometry) - FVC, FEV1, FEV1/FVC and PEFR.

The asthma control questionnaire: five items-shortness of breath, patient rating of control, use of rescue medication, work/school limitations related to asthma and nocturnal asthma symptoms, each of the five items assessed on a 5-point scale and the response is summed to give scores ranging from 5 (poor control) to 25 (complete control).

Tolerability was assessed by:

• Adverse drug reactions reported voluntarily by the patients, observed or enquired were recorded.

A baseline measurement of spirometry parameters was done, and both the groups were followed up at 4, 8, and 12 weeks for the outcome measurement.

# Statistical analysis

The data obtained was analyzed using the SPSS software version 22. Descriptive statistics including the mean and

standard deviation were calculated for quantitative variables. Quantitative variables were compared with Chisquare test, Fisher exact test, Student's t-test. Charts were generated using MS-EXCEL and MS -WORD.

# **RESULTS**

Totally 60 patients suffering from mild to moderate persistent bronchial asthma patients were evaluated and analyzed for epidemiological profile, disease spectrum, efficacy and tolerability parameter.

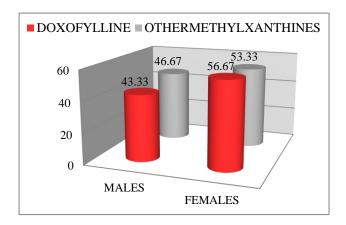


Figure 1: Gender wise distribution of patients studied.

In the present study, majority of the patients were females 56.6% and 53.3% compared to males 43.33% and 46.67%

in doxofylline and other methylxanthines group respectively.

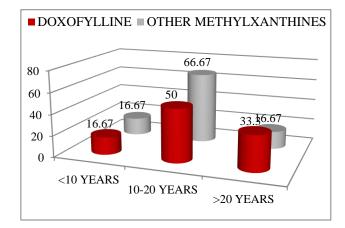


Figure 2: Duration of illness (years) in the two groups.

Mean duration of illness was 17.5 and 15.17 years in doxofylline and the other methylxanthines group respectively.

The asthma control test questionnaire revealed statistically significant improvement in both the groups compared to the baseline from 2<sup>nd</sup> visit onwards. There was significant difference in the doxofylline group compared to other methylxanthines group throughout the study.

Table 1: Comparison of efficacy parameters in two groups of patients studied (Asthma control test questionnaire score).

Asthma control test questionnaire score				
	Doxofylline	Othermethylxanthines	P value	
Baseline	16.82±1.44	15.65±0.58	<0.001**	
1 <sup>st</sup> Visit	16.9±1.25	16.44±0.68	0.047*	
2 <sup>nd</sup> Visit	17.64±1.22	16.89±0.68	0.001**	
3 <sup>rd</sup> Visit	18.6±1.07	18.00±0.80	0.005**	
Significance from base line				
1st Visit	$\Delta$ = 0.08; P=0.351	<b>Δ</b> = 0.78; P=0.001**	-	
2 <sup>nd</sup> Visit	Δ= 0.82; P=0.001**	Δ= 1.23; P<0.001**	-	
3 <sup>rd</sup> Visit	Δ= 1.72; P=0.001**	Δ= 2.34; P<0.001**	-	

Table 2: Comparison of subjective rating of asthma control.

Subjective rating of asthma control				
Efficacy parameters	Doxofylline	Other methylxanthines	P value	
Baseline	58.22±3.11	56.97±5.00	0.155	
1 <sup>st</sup> Visit	61.72±2.51	63.02±2.73	0.022*	
2 <sup>nd</sup> Visit	65.64±1.66	66.44±3.05	0.116	
3 <sup>rd</sup> Visit	73.26±2.35	72.23±2.51	0.053*	
Significance from base line				
1 <sup>st</sup> Visit	Δ <sub>=</sub> 3.50; P<0.001**	<b>Δ</b> =6.05; P=0.001**	-	
2 <sup>nd</sup> Visit	Δ=7.42; P<0.001**	Δ=9.47; P<0.001**	-	
3 <sup>rd</sup> Visit	Δ=15.04; P<0.001**	Δ=15.26; P<0.001**	-	

Table 3: Comparison of forced vital capacity in the two groups of patients studied.

Forced vital capacity				
	Doxofylline	Othermethylxanthines	P value	
Baseline	2.58±0.46	2.72±0.44	0.136	
% Predicted of baseline	79.85±3.25	80.34±1.92	0.378	
1st Visit	2.64±0.47	2.78±0.45	0.132	
% Predicted of 1 <sup>st</sup> Visit	81.64±3.13	82.20±1.93	0.303	
2 <sup>nd</sup> Visit	7.57±34.55	2.82±0.46	0.370	
% Predicted of 2 <sup>nd</sup> Visit	83.06±2.99	83.34±2.02	0.593	
3 <sup>rd</sup> Visit	2.71±0.47	2.84±0.46	0.186	
% Predicted of 3 <sup>rd</sup> Visit	83.96±2.96	83.81±1.88	0.781	
Significance from base line				
1 <sup>st</sup> Visit	<b>△</b> =0.056; P<0.001**	Δ=0.06; P=0.001**	-	
2 <sup>nd</sup> Visit	Δ=0.102; P<0.001**	Δ=0.10; P<0.001**	-	
3 <sup>rd</sup> Visit	<b>△</b> =0.129; P<0.001**	Δ=0.11; P<0.001**	-	

Table 4: Comparison of forced expiratory volume at end of 1 second (FEV1) in the two groups of patients studied.

	Doxofylline	Othermethylxanthines	P value
Baseline	1.74±0.32	1.83±0.29	0.124
% Predicted of baseline	64.1±3.29	64.06±2.65	0.955
Post salbutamol	2.17±0.39	2.34±0.40	0.040*
% Predicted	80.04±3.31	81.27±3.63	0.089+
1st Visit	1.86±0.34	1.95±0.32	0.169
% Predicted of 1 <sup>st</sup> Visit	68.26±3.29	68.95±2.74	0.630
2 <sup>nd</sup> Visit	1.97±0.35	2.06±0.34	0.192
% Predicted of 2 <sup>nd</sup> Visit	72.58±3.2	71.97±2.89	0.347
3 <sup>rd</sup> Visit	2.1±0.39	2.19±0.36	0.205
% Predicted of 3 <sup>rd</sup> Visit	76.82±3.24	76.30±3.00	0.429
Significance from base line			
1 <sup>st</sup> Visit	Δ=0.43; P<0.001**	=0.504; P=0.001**	-
2 <sup>nd</sup> Visit	Δ=0.119; P<0.001**	=0.114; P<0.001**	-
3 <sup>rd</sup> Visit	<b>△</b> =0.235; P<0.001**	Δ=0.229; P<0.001**	-

The Subjective rating of asthma control revealed statistically significant improvement in both the groups compared to the baseline in every visit. There was significant improvement in the doxofylline group compared to the other methylxanthines group at 2ndvisit and at the end of the study.

On analyzing the Spirometric parameter, Forced Vital Capacity, showed significant improvement in both the study groups compared to the baseline at every visit. There was no statistically significant difference in between the two groups throughout the study, indicating comparable efficacy.

The Spirometric parameter, forced expiratory Volume at the end of 1 second, revealed significant improvement in both the study groups compared to the baseline at every visit. There was no statistically significant difference in between the two groups throughout the study, indicating comparable efficacy.

On analyzing, the Peak Expiratory Flow Rate (PEFR), study revealed significant improvement in both the study groups compared to the baseline at every visit. There was no statistically significant difference in between the two groups throughout the study.

Comparing the FEV1/FVC ratio in both the study groups revealed that there was no significant difference in between the groups throughout the study. There was statistically significant difference within the groups, compared to the base line at every visit.

In the present study, adverse drug reactions were noted in 10% and 28% of doxofylline and other methylxanthines group respectively. Incidence of overall adverse drug

reactions were significantly more associated with Other methylxanthines; Group with P=0.041\*. Among the

adverse reactions, headache was the most common followed by nausea and insomnia.

Table 5: Comparison of peak expiratory flow rate in the two groups of patients studied.

	Doxofylline	Othermethylxanthines	P value
Baseline	4.95±0.93	5.067±8.51	0.317
% Predicted of baseline	68.59±3.02	68.96±1.63	0.464
1st Visit	5.16±0.96	5.22±1.06	0.770
% Predicted of 1st Visit	71.12±3.02	71.31±1.62	0.719
2 <sup>nd</sup> Visit	5.33±1.01	5.35±1.12	0.926
% Predicted of 2 <sup>nd</sup> Visit	73.62±3.12	73.26±1.57	0.521
3 <sup>rd</sup> Visit	5.45±1.04	5.49±1.13	0.862
% Predicted of 3 <sup>rd</sup> Visit	75.3±3.21	75.10±1.53	0.731
Significance from base line			
1 <sup>st</sup> Visit	Δ=0.21; P<0.001**	Δ=0.15; P=0.001**	-
2 <sup>nd</sup> Visit Δ=0.38; P<0.001** Δ=0.37; P<0.001**		-	
3 <sup>rd</sup> Visit	<b>△</b> =0.497; P<0.001**	Δ=0.43; P<0.001**	-

Table 6: Comparison of FEV1/FVC in the two groups studied.

	Doxofylline	Othermethylxanthines	P value
Baseline	67.11±2.32	67.70±1.48	0.155
1 <sup>st</sup> Visit	70.48±2.08	70.21±1.99	0.545
2 <sup>nd</sup> Visit	73.7±2.18	73.07±1.95	0.167
3 <sup>rd</sup> Visit	76.86±2.82	77.35±2.26	0.383
Significance from base line			
1 <sup>st</sup> Visit	Δ=3.36; P<0.001**	Δ=2.36; P=0.001**	-
2 <sup>nd</sup> Visit	Δ=6.69; P<0.001**	Δ=5.22; P<0.001**	-
3 <sup>rd</sup> Visit	Δ=9.74; P<0.001**	Δ=9.50; P<0.001**	-

Table 7: Comparison of overall tolerability parameters (adverse drug reactions) in the two groups of patients studied.

	Doxofylline		Othermethylxanthines	
	No	%	No	%
Present	5	16.67	14	46.67
Absent	25	83.33	16	53.33

#### DISCUSSION

The present comparative study on efficacy and tolerability of doxofylline over other methylxanthines involving 60 patients diagnosed with mild to moderate persistent bronchial asthma as per the may2014 guidelines of Global strategy for diagnosis and prevention of bronchial asthma updated, who had given written informed consent were enrolled for a study of 12 weeks duration. The study was conducted at chest hospital over a period of 8 months during which patients were evaluated and analyzed for

epidemiological profile, disease spectrum, efficacy and tolerability parameters.

Maximum number of patients were between the age group 31 to 50 years with a mean age of 42 years in the doxofylline group and 38 years in other methylxanthines group. More than 96% of the study patients were from the urban region. Majority of the patients were females constituting 56% and 53% compared to males 43% and 46% in doxofylline and other methylxanthines group respectively as found in a study done by Aggarwal et al.<sup>5</sup>

# Efficacy parameters

In the present study, asthma control test questionnaire revealed statistically significant improvement in both the groups compared to the baseline from 2nd visit onwards. There was statistically very significant difference in the doxofylline group (p=0.005\* at the end of the study) compared to other methylxanthines group throughout the study. Thus, indicating better control of asthma in the

doxofylline group with an increase in the score from the baseline to 2.34 as compared to 1.72 in the other methylxanthines group. This is in consistent with the study by patel Y et al, on controller medications as add on therapy to ICS and LABA for bronchial asthma management, that showed significant improvement in ACT score at end of the study compared to baseline using montelukast, doxofylline and increased dose of ICS, but no difference in between the study groups.<sup>6</sup> ACT in particular has been found to be useful in the primary Health Care facilities in the developing countries.<sup>7</sup>

The subjective rating of asthma control in the study revealed statistically significant improvement of 15% at the end in both the groups compared to the baseline. There was significant improvement in the doxofylline group compared to the other methylxanthines group at 2<sup>nd</sup> visit (p=0.022) and at the end of the study.

There was statistically significant reduction at every visit, in the need for rescue medication (β2 agonist) in both the groups compared to the baseline. The reduction in the use of rescue medication compared to the baseline was 3.32puffs/day less in doxofylline group, as against reduction of 2.9puffs/day less in other methyxanthines group by the end of the study (p=0.001\*\*) suggesting better control in doxofylline compared to other methylxanthines group. Similar to a double blind randomized placebo controlled multicentric clinical trial conducted by Goldstein Mr et al, in 346 patients of chronic reversible bronchial asthma with four groups. Doxofylline 400mg. Theophylline 250mg t.i.d, Doxofylline 200mg t.i.d, and Placebo group, demonstrated a significant reduction in the frequency of asthma attack and in use of albuterol with doxofylline 400mg t.i.d, as compared to that of the ophylline (p < 0.05).

Spirometric analysis in this study revealed significant improvement in both the study groups compared to the baseline at every visit (p=0.001\*\*). There was no statistically significant difference in between the two groups throughout the study. Compared to the baseline, percentage predicted of FVC improved by 4% and 3.5% FEV1, improved by 12.7% and 12.2%, PEFR improved by 6.7% and 6.2% and FEV'1/FVC ratio improved by 9.7 and 9.5 in doxofylline and other methylxanthine groups respectively. Measurement of pulmonary function test in the placebo-controlled clinical trial by Goldstein and Chervinsky indicated that doxofylline 400mg t.i.d. is as effective as theophylline 250mg t.i.d. in improving the airflow obstruction, with significant increase in FEV1 (17%) statistically significant improvement in both the groups compared to the placebo. In a randomized controlled trial by Dolcetti A et al, comparing doxofylline over placebo revealed significant improvement in FEV1, (>20% after 2 hours) compared to baseline. The results in this study were in accordance to a double blind multicentre randomized trial, done by Melillo, G et al, that showed significant improvement in Spirometric parameters,

reduced salbutamol consumption with doxofylline and Theophylline.<sup>9</sup>

# Tolerability parameters

Tolerability of methylxanthines has always been an issue due to which, they have a consistent limitation in use, a newer methylxanthine with less adverse effect is in constant search in our study, a novel methylxanthine, doxofylline revealed significantly lower incidence of overall adverse drug reactions compared with other methylxanthines group with P=0.041\*. Adverse drug reactions were noted in 10% of doxofylline and 28% in other methylxanthines group. Among the adverse reactions noted, headache was the most common followed by nausea and insomnia. Adverse events like vomiting epigastric pain, palpitation and tachycardia was seen only in other methylxanthines group, nervousness was seen in both the groups.

Clinical trials have shown a decrease in the incidence of adverse effects with doxofylline in comparison with those observed with theophylline, demonstrating an increased safety. Doxofylline has shown a better tolerability than theophylline and aminophylline in a study by Bossi. F et al, the probable reasons for better tolerability with doxofylline, could be due to low affinity for adenosine receptors (A1 and A2), it does not interfere with calcium flux through the cellular membrane nor antagonizes calcium channel antagonists that differentiate it from theophylline. The effective therapeutic dose of doxofylline has less cardio stimulant effect than theophylline, which allows its use without significantly increasing the cardiac frequency without arrhythmogenic effect. The strength of the

It has also been demonstrated that Theophylline interferes with gastric secretion and gastrointestinal (GIT) motility, increasing the secretion of hydrochloric acid and pepsin in the stomach and reducing the pressure in the inferior esophageal sphincter, facilitating the development of gastroesophagic reflux. Doxofylline, on the other hand, does not increase the acid or pepsin output, reflected in the occurrence of fewer GI side effects. It has been suggested that this would make doxofylline better tolerated than theophylline in patients with peptic ulcer disease. <sup>12</sup>

Theophylline produces alterations in the structure and quality of sleep causing insomnia and many awakenings. In a study by Sacco et al, the number of arousals per night when treated with theophylline was almost double compared to when the subjects did not receive any medication, doxofylline did not result in more arousals. All subjects experienced REM sleep (Rapid Eye Movement) with doxofylline, then when treated with theophylline where only 50% of the subjects experienced REM sleep. This reduction in the quality of sleep does not occur among patients treated with doxofylline, who in addition experienced less restlessness. On comparing the recommended dose of doxofylline and its maximum dose,

better tolerability was seen with doxofylline than with theophylline. 13

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