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COMPARATIVE STUDY OF DOXOFYLLINE OVER OTHER METHYLXANTHINES AS ADD-ON THERAPY TO INHALED CORTICOSTEROIDS IN STABLE ASTHMA PATIENTS

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ABSTRACT **Background:** Doxofylline is a novel methylxanthine with effects similar to other members of the group and with certain advantages over them. The present study aims to compare the efficacy and safety of the same over other members of the methylxanthine group. **Methods:** The study was observational and prospective of one year duration (December 2018-2019) and was conducted at Nalanda Medical College and Hospital. A total of 100 patients diagnosed with mild to moderate persistent asthma stable at the time of presentation with FEV1 50% or more of the predicted were included in the study. Half of them were given doxofylline and the remaining half were furter subdivided into two groups to be given theophylline and fixed dose combination of etofylline and theophylline respectively and the results were noted. Efficacy was assessed by monitoring the Pulmonary Function Test (PFT) values [– Forced Vital Capacity (FVC), Forced Expiratory Volume in 1 sec (FEV1), FEV1/FVC and Peak Expiratory Flow Rate (PEFR)] and by subjective assessment of disease control by Asthma Control Test questionnaire. Tolerability was assessed by voluntary reporting of adverse effects by the patients and also those observed and enquired. **Results And Conclusion:** The present study demonstrated that Doxofylline was comparable to other methylxanthines in improving the PFT parameters over subsequent visits though it was statistically better in improving the subjective control of asthma (ACT scores). Also, the patients experienced fewer side effects with doxofylline when compared to the other group. Thus, we conclude that doxofylline could be a better and safer option to other methylxanthines in treating asthma patients.

KEYWORDS : Efficacy, Safety, Doxofylline, Methylxanthines

INTRODUCTION

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation and is defined by history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and intensity, together with variable expiratory airway limitation[1]. It is diagnosed mainly by clinical history, physical examination and more objectively by pulmonary function testing including reversibility test.

Asthma is prevalent worldwide with more than 339 million sufferers[2]. It is a major public health concern for all countries alike, irrespective of the level of development. Data on prevalence in India are inconsistent. However, it has been estimated to be about 2%[3] with around 1/10th of total asthmatics living in India[4].

As bronchial asthma is a non-curable disease, the goal of management is the achievement and maintenance of control of symptoms, reducing risk of future exacerbations and the attainment of best possible quality of life for the patients. The pharmacotherapy for asthma is aimed at suppression of inflammation and reduction of bronchial hyperreactivity and airway obstruction. The medications are broadly divided into two groups – Controllers (for maintenance therapy) and Relievers (for symptomatic relief on as-needed basis). The Controller medications include the inhaled corticosteroids which form the mainstay of treatment, inhaled long-acting β2 agonists (LABA), leukotriene receptor antagonists, anti-IgE, anti IL-5/5R, anti IL-4R, xanthine derivatives, chromones and systemic corticosteroids. The Reliever medications include the inhaled short-acting β2 agonists, low-dose ICS- formoterol and inhaled anticholinergics.[1]

Methylxanthines are a unique class of drugs with various mechanisms of action – phosphodiesterase inhibition, adenosine receptor antagonism and effects on histone-deacetylase activity being the notable ones. They have bronchodilator, immunomodulatory, anti-inflammatory and bronchoprotective roles[5].

Theophylline, a methylxanthine has been used traditionally and widely but studies have found that it has only weak efficacy in asthma[6,7,8] with very narrow therapeutic window and several drug-drug interactions leading to various side-effects; may be even life-threatening in high doses[9]. The numerous adverse effects, various drug-drug interactions and the need for regular plasma monitoring are major limitations of this drug[10].

Doxofylline, a novel methylxanthine, differs from theophylline in containing the dioxolane group at position 7 and has been found to have both anti-inflammatory and bronchodilating properties. Its clinical efficacy in asthma is comparable to that of theophylline with improved safety profile. Better safety profile of this drug can be attributed to its reduced affinity towards adenosine A_1 and adenosine A_2 receptors and also the major differences in pharmacological profile of the two drugs.

Unlike theophylline, doxofylline lacks the ability to interfere with the cytochrome enzymes CYP1A2, CYP2E1 and CYP3A4, thus avoiding several unwanted interactions with other drugs metabolized via these pathways in liver[11].Also, the serum concentrations produced by doxofylline are more stable and do not correlate with the occurrence of adverse events; so, no need for continued or repeated blood level monitoring either with low-dose or high-dose doxofylline.

Nowadays, a number of inhaled devices and drug formulations are available for the treatment of asthma which are safe as well as effective but are expensive and often associated with poor adherence. Thus, there is a need for drugs that are active orally and are safe apart from being affordable for many. Doxofylline is one such drug. The present study is aimed to compare the efficacy and safety of doxofylline over other methylxanthines like theophylline as add-on therapy in stable asthma patients on inhaled corticosteroids.

MATERIALS AND METHODS

A total of 100 patients diagnosed with mild to moderate persistent asthma (clinically stable at the time of presentation) attending Medicine Outpatient Department of Nalanda Medical College and Hospital, Patna, Bihar were included in the study.

The study was observational and prospective of one year duration (from December 2018- November 2019).

Inclusion Criteria:

- Patients giving informed consent.
- Patients of either sex aged between 18-65 years.
- Patients diagnosed with mild to moderate persistent asthma clinically stable at the time of presentation.
- Patients on inhaled corticosteroids.
- Patients with FEV1 (Forced Expiratory Volume in the first second of expiration) value of 50% or more of predicted.

Exclusion Criteria:
- Patients not giving consent.
- Patients with severe disease / on systemic corticosteroids.
- Patients with major respiratory illness other than asthma like Chronic obstructive pulmonary disease.
- Patients with co-morbid conditions like Ischaemic heart disease, congestive cardiac failure, renal or hepatic dysfunction; neurological, endocrinal and hematological abnormalities.
- Smokers, pregnant and lactating women.
- History of known allergy/intolerance/hypersensitivity to study drugs.
- Patients on regular treatment with drugs that interact with methylxanthines.

METHODS:
- Institutional ethics committee approval was taken.
- Informed consent was taken from all the study participants.
- The patients fulfilling the inclusion as well as exclusion criteria were included in the study and the study findings recorded in two groups (each comprising of 50 patients):

Group 1: Patients treated with Doxofylline 400mg BD orally for eight weeks
Group 2: Patients treated with other methylxanthines:
- Theophylline 300mg BD orally for eight weeks
- Fixed dose combination of Etofylline (115mg) and Theophylline (35mg) BD orally for eight weeks

- Demographic data, history, clinical examination and details of drug prescription by the treating physician were recorded. Relevant laboratory investigations were done at the beginning and at the end of the study.
- Efficacy was assessed by:
- Pulmonary Function Test (Spirometry) parameters - FVC, FEV1, FEV1/FVC and PEFR.
- The Asthma control questionnaire: This questionnaire consists of five items-

1) shortness of breath
2) patient rating of control
3) use of rescue medication
4) work/school limitations related to asthma
5) nocturnal asthma symptoms

Each of the five items is 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 effects reported voluntarily by the patients, observed or enquired were noted.

Follow-up:
The patients were followed up after four weeks and then after eight weeks of the initial visit and the findings noted.

Statistical Methods:
- The data entered was analyzed with descriptive studies; and specific statistics were applied.
- The data was analyzed in SPSS version v.22 and the results were recorded in percentages, independent t-test and paired t-test.
- Before conducting the t-test, Levenys test was performed to decide the homogeneity of equal variances.
- P-value of <0.05 was taken as statistically significant, otherwise non-significant.

RESULTS
The mean age of patients in the Doxofylline group was 45 years while in Othermethylxanthines group was 44 years. Maximum number of patients were in the 18-30 years and 41-50 years age group respectively. Majority of patients were females (53% of total). In the Doxofylline group, there were 54% females and 46% males while in the Othermethylxanthines group there were 52% females and 48% males.

Table 1. Comparison Of Forced Vital Capacity In The Two Groups Of Patients Studied

FVC visit	Doxofylline	Othermethylxanthines	T value	DF	P-value
FVC Visit 1 (Baseline)	2.56 +/- 0.71	2.65 +/- 0.63	0.662	98	0.507
FVC visit 2	2.74 +/- 0.79	2.7 +/- 0.68	0.257	98	0.798
P-value (Within Group visit 1/visit 2)	<0.001	0.046			
FVC visit 3	2.90 +/- 0.81	2.77 +/- 0.68	0.91	98	0.366
P-value (within group visit1/visit 3)	<0.001	<0.001			

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.

Table 2. Comparison Of Mean Forced Expiratory Volume In 1 Second In The Two Groups Of Patients Studied

FEV1 Visit	Doxofylline	Othermethylxanthines	T value	DF	P-value
FEV1 visit1 (Baseline)	1.6566 +/- .50242	1.7246 +/- .47780	0.694	98	0.490
FEV1 visit 2	1.8102 +/- .56712	1.8234 +/- .54907	0.118	98	0.906
P-value (Within Group visit 1/visit 2)	<0.001	<0.001			
FEV1 visit 3	1.99 +/- 0.57	1.93 +/- 0.58	0.474	98	0.637
P-value (within group visit 1/visit 3)	<0.001	<0.001			

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.

Table 3. Comparison Of Mean Peak Expiratory Flow Rate In The Two Groups Of Patients Studied

PEFR Visit	Doxofylline	Othermethylxanthines	T value	DF	P-value
PEFR visit1 (Baseline)	4.1386 +/- 1.49670	3.9308 +/- 1.39469	0.718	98	0.474
PEFR visit 2	4.4376 +/- 1.54854	4.2426 +/- 1.49378	.641	98	0.523
P-value (Within Group visit 1/visit 2)	0.462	0.001			
PEFR visit 3	4.68 +/- 1.57	4.40 +/- 1.5	0.89	98	0.373
P-value (within group visit 1/visit 3)	0.164	<0.001			

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.

Table 4. Comparison Of Mean Fev1/fvc In The Two Groups Of Patients Studied

FEV1/FVC Visit	Doxofylline	Othermethylxanthines	T value	DF	P-value
FEV1/FVC visit 1 (Baseline)	77.78 +/- 8.67	77.42 +/- 8.22	0.213	98	0.832
PEFR visit 2	79.62 +/- 10.14	80.34 +/-	0.373	98	0.710
P-value (Within Group visit 1/visit 2)	0.003	0.001			

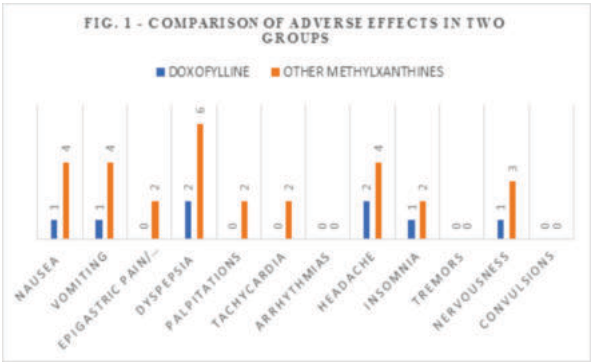
PEFR visit 3	80.56 +/- 9.55	81.24 +/- 8.77	0.371	98	0.711
P-value (within group visit 1/visit 3)	<0.001	<0.001			

The spirometric parameter, FEV1/FVC ratio, 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.

Table 5. Comparison Of Mean Asthma Control Test Questionnaire Score

	Doxofylline	Othermethylxanthines	p-value
Baseline	17.72	17.86	0.758
Final	20.16	19.06	0.032
Significance from baseline	p-value<0.001	p-value<0.001	

The Asthma control test questionnaire score revealed statistically significant improvement in both the groups compared to the baseline (p-value< 0.001). Also, there was significant difference in the two groups with doxofylline having better score at the end of the study.



In the present study, adverse effects were noted in 16% and 22% of patients in Doxofylline and Othermethylxanthines group respectively while the incidence of adverse effects was 16% and 59% in the respective groups. Among the adverse effects, dyspepsia was the most common followed by headache.

DISCUSSION

In the present study, the mean age of patients were 45 years and 44 years in the Doxofylline and the Othermethylxanthines group, respectively with maximum number of patients in 41-50 years age group. This is similar to the findings of the study conducted by Satyendra K. Alladi et al with mean age of 42 years and 38 years in respective groups with majority of patients in 31-50 years age group[12]. Majority of patients were females in both groups; 54% and 52% females compared to 46% and 48% males in both groups, respectively which is in accordance with many previous studies[13,14].

Efficacy parameters:

The present study demonstrated that the spirometric variables FVC, FEV1, FEV1/FVC and PEFR showed a significant improvement over baseline in subsequent visits with the use of both Doxofylline and Othermethylxanthines groups. In the Doxofylline group, the percentage predicted of FVC improved by 7.6%, FEV1 by 8.2%, FEV1/FVC by 2.78% and PEFR by 3.82% while in the Othermethylxanthines group these parameters changed by 2.34%, 5.28%, 3.82% and 7.38%, respectively. These changes were significant in both the study groups when compared with the baseline at every visit, however, there was no statistical difference when the data was compared in between the two groups throughout the study. The results of the present study correlates well with that of previous studies[12,15].

In the present study, Asthma control test (ACT) questionnaire score revealed statistically significant improvement in both groups at the end of the study from baseline. Also, there was statistically significant difference in between the two groups; Doxofylline being better. This correlates well with the results of another study conducted by Alladi et al[12]. A recent literature review conducted by van Dijk et al concluded ACT to be an appropriate measure for overall asthma control[16]. ACT has also been found to be particularly useful in resource-limited settings such as Primary Health Care facilities in the developing countries[17]. Thus, it can be safely said that doxofylline resulted in better overall asthma control as perceived by the patients compared to other drugs used in the study.

Tolerability parameters:

In the present study, Doxofylline showed an improved safety profile as compared to Other methylxanthines. Adverse effects were noted in 16% and 54% of the patients in the two groups respectively. Among the various adverse effects, dyspepsia was the most common followed by headache. Other adverse effects like epigastric pain/ discomfort, nausea, vomiting, insomnia and nervousness were seen in patients with both groups but were more common with methylxanthines other than Doxofylline.

Various clinical trials have shown that there is a decrease in the incidence of adverse effects with doxofylline when compared with other methylxanthines. Doxofylline has been shown to have a lower secretagogue activity than aminophylline in patients with endoscopically-proven healed duodenal ulcers[18] and also superior gastric tolerability than theophylline[19].

In a study by Sacco et al, it was reported that the number of arousals per night was more when patients were treated with theophylline while doxofylline did not result in any significant increase in such events when compared to no treatment. Theophylline also led to significant disruption of sleep architecture and quality while doxofylline had minimal impact on the same[20].

Doxofylline has also been shown to have lesser cardio-stimulant action as compared to theophylline and hence, lesser arrhythmogenic potential[21].

Our study thus, suggests that doxofylline has efficacy comparable and safety /tolerability profile better than that of other methylxanthines used in the study. Several trials have shown similar results[12,15] while a very recent meta-analysis comparing the efficacy and safety profile of doxofylline to that of theophylline in asthma has concluded that doxofylline is an effective and safe methylxanthine for the treatment of asthma, and that its efficacy/safety profile is better than that of theophylline[22].

CONCLUSION

Methylxanthines are a unique class of drugs with bronchodilator, immunomodulator, anti-inflammatory, bronchoprotective, mucoregulatory, inflammatory cell stabilizing and steroid sparing properties. The present study revealed that treatment with methylxanthines produced significant bronchodilatation in both the groups compared to baseline when used as an add-on therapy to inhaled corticosteroids in stable asthma patients.

Doxofylline was found to be equally efficacious to other methylxanthines (theophylline and FDC of etophylline and theophylline) when compared in terms of the spirometric parameters and it even fared better when compared in terms of Asthma control test questionnaire score thus revealing a better subjective control of asthma symptoms.

In terms of tolerability, doxofylline was significantly better than other methylxanthines used in the study. Dyspepsia was the most common side effect followed by headache, nausea, vomiting, insomnia and nervousness. All these side effects were seen in both groups but were more frequent with methylxanthines other than doxofylline. Palpitations and epigastric discomfort were seen only in the Othermethylxanthines group.

Based on the results of our study, it can be concluded that doxofylline has comparable efficacy and better safety profile when compared to other methylxanthines used in the study and thus, can be considered as a better alternative in the treatment of patients with mild to moderate asthma as an add-on therapy to inhaled corticosteroids.

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