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ORIGINAL ARTICLE

Comparative study of Doxophylline and Theophylline in Stable COPD Patient Regarding Efficacy and Safety

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Abstract:

Background: *Doxophylline and Theophylline are xanthine bronchodilator but Doxophylline differs from Theophylline in that it contains a dioxalane group in position 7. Similarly to Theophylline, its mechanism of action is related to the inhibition of phosphodiesterase activities, but in contrast it appears to have decreased affinities towards adenosine A1 and A2 receptors, which may account for its better safety profile. The current study was designed to compare the efficacy and safety of doxophylline and theophylline, in patients with chronic obstructive pulmonary diseases.*

Methods: *It was a randomized, prospective and single blind study conducted at the department of Respiratory Medicine in National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka.Eighty patients were randomly assigned to an 8-week oral treatment with either doxophylline 200 mg b.i.d. or theophylline 200 mg b.i.d. Pulmonary function tests (PFTs) were performed at 4 and 8 weeks of treatment. Among them, 31 patients in doxophylline group and 30 patients in theophylline group came to final follow-up.*

Results: *The baseline spirometric variables were similar and not statistically significant in the study groups. Both the drugs significantly improved spirometric variables. The improvement in FEV1 was statistically significant as compared to the value at the baseline. The improvement was statistically significant at every visit (i. e. at 4 week and at 8 week) as compared to the baseline. After 4 weeks of treatment both the groups experienced side effects including nausea, dyspepsia, irregular pulse, headache and insomnia without any significant difference while after 8 weeks patients in theophylline group suffered significantly more from palpitation than doxophylline group.*

Conclusion:*Doxophylline had a favorable tolerability profile that suggests that this drug might be of particular benefit in COPD patients.*

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Introduction:

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airway and the lung to noxious particles or gases (Rabe et al. 2007)Theophylline (1, 3 dimethyl xanthine) has been used in the treatment of COPD for decades.Bronchodilatation is main stay of treament in COPD patient. Bronchodilatation occurs in the serum theophylline concentration range of 5-20 ìg/ml. Adverse reactions i.e. vomiting, headache, cardiac arrhythmias and seizures occur when the peak serum concentration exceeds 20 ìg/ml. Doxophylline 7- (1, 3 dioxolane-2-yl methyl) is a newer xanthine derivative which differs from theophylline in containing the dioxalane group at position 7. Similarly to theophylline, its mechanism of action is related to the inhibition of the phosphodiesterase enzymes. It has been claimed to have decreased affinities towards the adenosine A1 and A2 receptors, which has been claimed as a reason for its better safety profile. The bronchodilating activities of Doxophylline have been demonstrated in clinical trials involving patients with COPD. There are only few studies which have been done on doxophylline in patients of COPD and comparable studies with theophylline are further an exceptional entity. Hence, it was considered worthwhile to do a comparative study of theophylline and doxophylline at the commonly used doses, for evaluating their efficacy and safety in patients of COPD.

Subject and methods:

This study was conducted in National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali,Dhaka. This was a single-blind, randomized, prospective, study with initial screening of patients that included 4-weeks intensive investigation and management phase (run in period), followed by baseline, 4 weekly for 8 weeks follow-up phase to determine the FEV1, and CAT score change of stage-II COPD patients to see the efficacy. 4 weekly for 8 weeks follow-up phase to determine the common adverse events (Nausea, Dyspepsia, Irregular pulse, Palpitaion, Headache, Insomnia)

Inclusion criteria:

- Post Bronchodilator FEV1/FVC <70%
- COPD stage- II
- Age- 40 to 75 years.
- Stable COPD for the last 1 month.

Exclusion criteria:

- Acute or chronic cardiac disease.
- Exacerbation of COPD within 1 month.
- Long-term oxygen therapy.
- Arterial oxygen saturation <88% at rest.
- Refused to enroll in the study.

Sampling method:

The study protocol was approved by institutional ethics committee of NIDCH and an informed consent of all the patients was taken before enrolling them in the study. The sample size was calculated and total 80 sample was taken. Sample patients were divided into two groups by simple randomization.

– One group was given Tab. Doxophylline 400 mg daily for oral intake in addition of their standard management (Inhaled Tiotopium- 18 mic.gm, Salmeterol- 50 mic.gm and Fluticasone- 500mic.gm) for consecutive 8 weeks. (Group-1)

– Another group was given Tab. Theophylline in addition of their standard management (Inhaled Tiotopium- 18 mic.gm, Salmeterol- 50 mic.gm and Fluticasone- 500mic.gm) for consecutive 8 weeks. (Group-2)

Study Procedure:

This was a single-blind, randomized, prospective, study with initial screening of patients that included 4-weeks intensive investigation and management phase (run in period), followed by baseline, 4 weekly for 8 weeks follow-up phase to determine the FEV1, and CAT score change of stage-II COPD patients to see the efficacy. 4 weekly for 8 weeks follow-up phase to determine the common adverse events (Nausea, Dyspepsia, Irregular pulse, Palpitaion, Headache, Insomnia). Patients were recruited from the indoor and outpatients department of National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali,Dhaka. 80 patients with COPD

(defined by specific criteria) were reviewed and if inclusion and exclusion criteria fulfilled, written consent was taken and were registered for the study and data were collected. Lung function test in the form of spirometry, CAT score done at baseline. Patients then subjected to randomize into 'Group-1' and 'Group-2'. Both groups were given standard treatment of COPD. All patients were assessed at 4 weekly for 8 weeks by Spirometry, CAT score and ECG with the base line values to see the efficacy. To evaluate the safety of doxophylline and theophylline all patients were assessed at 4 weekly for 8 weeks for common adverse events (Nausea, Dyspepsia, Irregular pulse, Palpitaion, Headache, Insomnia) .Finally 31 patients in group-1 and 30 patients in group-2 came to final follow up. In group-1, 9 patients had lost to follow up, in group-2, 9 patients had lost to follow up and 01 patient died. All the information were properly documented in the prescribed form.

Results:

This randomized, prospective and single blind study was done to see the efficacy and safety of Doxophylline in COPD patient . For this purpose 80 patients having COPD who were admitted in the National Institute of Diseases of the Chest and Hospital were enrolled on the basis of selection criteria. Half of the patients were treated by theophylline and the other half with doxophylline by random allocation. The findings derived from the data analysis are presented here:

Table-I

Comparison of different FEV1 score between theophylline and doxophylline groups

Parameter	Group	Mean	t-value	df	p-value*
Baseline FEV1 (% of predicted)	Doxophylline	53.80	0.912	70.07	0.365
	Theophylline	53.05			
At 4 week FEV1 (% of predicted)	Doxophylline	55.13	1.196	69.60	0.236
	Theophylline	54.20			
At 8 week FEV1 (% of predicted)	Doxophylline	55.93	1.375	70.47	0.173
	Theophylline	54.90			

Table-II

Comparison of different CAT score between theophylline and doxophylline groups

Parameter	Group	Mean	t-value	df	p-value*
Baseline CAT score	Doxophylline	15.98	-.111	77.98	0.912
	Theophylline	16.00			
At 4 wk CAT score	Doxophylline	15.70	0.453	75.0	0.652
	Theophylline	15.60			
At 8 wk CAT score	Doxophylline	15.50	0.397	74.67	0.693
	Theophylline	15.43			

Table-III

Number of subjects with adverse drug events at 4 weeks and their comparison

Side effects at 4 weeks	Status	Group		χ^2	p-value*
		Doxophylline (n=35) n (%)	Theophylline (n=33) n (%)		
Nausea	Present	03 (8.6)	04 (12.1)	0.232	0.630†
	Absent	32 (91.4)	29 (87.9)		
Dyspepsia	Present	04 (11.4)	03 (9.1)	0.105	0.751†
	Absent	31 (88.6)	30 (90.9)		
Irregular pulse	Present	02 (5.7)	04 (12.1)	0.866	0.352†
	Absent	33 (94.3)	29 (87.9)		
Palpitation	Present	06 (17.1)	11 (33.3)	2.375	0.123
	Absent	29 (82.9)	22 (67.7)		
Headache	Present	03 (8.6)	03 (9.1)	0.0057	0.939†
	Absent	32 (91.4)	30 (90.9)		
Insomnia	Present	06 (17.1)	8 (24.2)	0.523	0.469
	Absent	29 (82.9)	25 (75.8)		

Table-IV

Number of subjects with adverse drug events at 8 weeks and their comparison

Side effects at 8 weeks	Status	Group		χ^2	p-value*
		Doxophylline (n=31) n (%)	Theophylline (n=30) n (%)		
Nausea	Present	4 (12.9)	8 (26.7)	1.828	0.176†
	Absent	27 (87.1)	22 (73.3)		
Dyspepsia	Present	4 (12.9)	7 (23.3)	1.122	0.289†
	Absent	27 (87.1)	23 (76.7)		
Irregular pulse	Present	2 (6.5)	5 (16.7)	0.021	0.886†
	Absent	29 (93.5)	25 (83.3)		
Palpitation	Present	5 (16.1)	12 (40.0)	4.321	0.037
	Absent	26 (83.9)	18 (60.0)		
Headache	Present	4 (12.9)	4 (13.3)	0.003	0.960†
	Absent	27 (87.1)	26 (86.7)		
Insomnia	Present	6 (19.4)	7 (23.3)	0.144	0.704
	Absent	25 (80.6)	23 (76.7)		

The mean age of the patients of theophylline group was 53.6 (±4.8) years while that of the doxophylline group was 53.78 (±5.5) years. Most of the patients in theophylline group were male (95%). Only 2 patients (5%) were female. Most of the patients in doxophylline group were male (82%). Only 7 patients (18%) were female. In Theophylline group 20(50%) patient were taken from indoor and another 50% patients from outdoor. In Doxophylline group most of the patients were from indoor (25, 62.5%)) and 15 were from outdoor. Comparison of improvement by FEV1 between theophylline and doxophylline groups from baseline to 4 week was done. In doxophylline group the mean FEV1 (% of predicted) increased from 53.8% to 55.13% after 4 weeks. In theophylline

group the mean FEV1 (% of predicted) also increased from 53.05% to 54.2% after 4 week. Comparison of improvement by FEV1 between theophylline and doxophylline groups from baseline to 8 week showed that In doxophylline group the mean FEV1 (% of predicted) increased from 53.8% to 55.93% after 4 week from baseline. In theophylline group the mean FEV1 (% of predicted) also increased from 53.05% to 54.9% after 8 week. Improvement of FEV1 between theophylline and doxophylline groups from 4 week to 8 week is compared. In doxophylline group the mean FEV1 (% of predicted) increased from 53.13% (4 week) to 55.93% (8 week). In theophylline group the mean FEV1 (% of predicted) also increased from 53.2% to 54.9% in this 4 weeks time. Comparison of improvement by CAT score between theophylline and doxophylline groups from baseline to 4 week showed that In doxophylline group the mean CAT score decreased from 15.98 to 15.70 after 4 week. In theophylline group the mean CAT score also decreased from 16.00 to 15.60 after 4 weeks. Both these differences were statistically highly significant ($p<0.001$). Improvement by CAT score between theophylline and doxophylline groups from baseline to 8 week is compared. In doxophylline group the mean CAT score decreased from 15.98 (baseline) to 15.50 (8 week). In theophylline group the mean CAT score also decreased from 16.00 to 15.43 after 8 weeks from baseline. Both these differences were statistically highly significant ($p<0.001$). Improvement by CAT score between theophylline and doxophylline groups from 4 week to 8 week was compared. In doxophylline group the mean CAT score decreased from 15.70 (4 week) to 15.50 (8 week). In theophylline group the mean CAT score also decreased from 15.60 to 15.43. Both these differences were statistically significant ($p<0.05$). The ccomparison of different FEV1 score between theophylline and doxophylline group showed at baseline the mean FEV1 (% of predicted) of both groups were almost equal and not different statistically. Like baseline value the 4 and 8 weeks values of mean FEV1 (% of predicted) were slightly higher in doxophylline group than theophylline group but statistically non significant ($p>0.05$).In comparison of different CAT scores between theophylline and doxophylline groups baseline mean CAT scores of both groups were almost equal and not different statistically ($p>0.05$). Like baseline value the 8 weeks value of the mean CAT scores were slightly lower in doxophylline and slighly higher in doxophylline group than theophylline group but statistically non significant ($p>0.05$). Numbers of subjects with adverse drug events at 4 weeks were compared between theophylline and doxophylline groups. After 4 weeks of treatment both the groups experienced side effects including nausea, dyspepsia, irregular pulse, palpitation, headache and insomnia without any significant difference ($p>0.05$). Numbers of subjects with adverse drug events at 8 weeks were compared between theophylline and doxophylline groups . At this stage patients in theophylline group suffered significantly more from palpitation than doxophylline group ($p<0.05$). Other side effects occurred in the two groups without any significant difference ($p>0.05$).

Discussion:

The results of the study showed improvement in FEV1 was statistically significant at every visit (i. e. at 4 week and at 8 week) as compared to the baseline. Our results are consistent with those of previous studies that assessed the effects of orally administered doxophylline in the management of patients with chronic obstructive airway diseases. Melillo et al. (1989) examined the clinical effects of doxophylline in 139 patients with chronic airway obstruction treated in a double-blind randomized fashion with either doxophylline 400 mg b.i.d. or theophylline 300 mg slow-release b.i.d. Both doxophylline and theophylline treatments significantly improved all pulmonary function parameters as compared to baseline ($p<0.05$), but were not statistically different from each other. In another randomized, prospective and open label study (Akram et al. 2012) , a total of 154 patients were divided in two group. Group I was administered 400 mg theophylline SR once daily and group II was administered doxophylline 400 mg twice a day orally. Spirometric variables symptom score were recorded on day 0, 7 and 21 of therapy. Results of the study showed that there was no statistically significant difference with respect to spirometric variables and symptom score in the two groups which was similar to my study result. After 8 weeks of treatment both groups experience nausea and dyspepsia as GIT

side effect but without any significant difference (p>0.05). Although in some study by Barnes et.al. (1994), Grossi et.al (1988), Melillo et al. (1989) found that doxophylline has less significant GIT side effect than theophylline which was dissimilar from my study findings. But, Akram et al.(2012) observed no significant difference in GIT side effect between doxophylline and theophylline which was consistent with my study. After 4 weeks of treatment both the groups experienced side effects of CVS , irregular pulse, palpitation, without any significant difference (p>0.05) while after 8 weeks patients in theophylline group suffered significantly more from palpitation than doxophylline group (p<0.05). The number and frequency of adverse events in the study population was similar to that of previous comparative studies of xanthine medications in COPD patients (Dini 1993; Chapman et al. 1994, Cipri et al. 1992). In accordance with previous studies (Barnes et al. 1994; Grossi et al. 1988), CNS adverse events headache, insomnia were more common with theophylline than doxophylline and also statistically significant which was not resemble of my study findings. . But, Akram et al. (2012) observed no significant difference in CNS side effect between doxophylline and theophylline which was consistent with my result. It is well known that theophylline is effective in the chronic management and the maintenance therapy of COPD. Doxophylline produces an improvement in the airway obstruction as theophylline. The data from this study showed that doxophylline 200 mg twice a day was not only as effective as theophylline 200 mg twice daily in the treatment of COPD but also it exhibited less drug related toxicities.

Conclusion: This clinical study showed that doxophylline 200 mg b.i.d. is as effective as theophylline 200 mg b.i.d. in the treatment of COPD. Doxophylline has shown two characteristics that may expand its usefulness in the clinical setting. First, it produces improvements in airflow obstruction similarly to theophylline and associated with a reduction in the prevalence of COPD attacks. Second, it has a favorable tolerability profile that suggests that this drug might be of particular benefit in selected groups of patients, especially those with cardiac intolerance to theophylline. Since doxophylline was associated with remarkable bronchodilatory response, symptom relief and potentially less adverse events, it seems to offer a promising alternative to theophylline therapy in the management of COPD patients.

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