Doxofylline and Theophylline: A Comparative Clinical Study

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ABSTRACT

Objectives: COPD is one of the major public health problems worldwide. Theophylline has been used in the treatment of COPD for decades. Doxofylline, a new Theophylline congener, has been claimed to have better safety profile. The study was undertaken to compare Theophylline and doxophylline at doses recommended and commonly used in clinical practice.

Methods: The study was conducted in patients of COPD in TB chest department of a medical college hospital. It was randomized, prospective and open label. A total of 154 patients were divided into two groups. Group I was administered 400 mg Theophylline SR once daily and group II was administered

Doxofylline 400 mg twice a day orally. Spirometric variables, symptom score and adverse effects were recorded on day 0, 7 and 21 of therapy. Data were compared and analysed using SPSS version 16.

Results: Results of the study showed that there was no statistically significant difference with respect to spirometric variables and symptom score in the two groups and there was no significant difference in two groups with respect to side-effects (p>0.05).

Conclusion: It is concluded that Doxophylline has no advantage over Theophylline in terms of either efficacy or safety on the doses commonly used in current clinical practice.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is one of the major public health problems in the world. The World Health Organization (WHO) has estimated that COPD is currently the seventh leading cause of death and disability worldwide [1]. The airflow obstruction in COPD is associated with the abnormal inflammatory response of the lungs to the chronic inhalational exposure from smoke, dust and other air pollutants. Chronic obstructive pulmonary disease which includes chronic bronchitis and emphysema, is a progressive disease which is characterized by airflow limitation/obstruction, that is, either not reversible at all or only partially reversible [2].

Theophylline (1, 3 dimethyl xanthine) has been used in the treatment of asthma and COPD for decades. Apart from the inhibition of PDEs, some other mechanisms have also been proposed, especially its anti-inflammatory activity through the activation of Histone Deacetylases (HDAC), that seem to be important for COPD and asthma inflammation [2,3]. Bronchodilatation occurs in the serum Theophylline concentration range of 5-20 μg/ml. Adverse reactions, e.g. vomiting, headache, cardiac arrhythmias and seizures occur when the peak serum concentration exceeds 20 μg/ml.

Doxofylline 7- (1, 3 dioxolane-2-yl methyl) is a newer xanthine derivative which differs from Theophylline in containing the diosalane group at position 7. As with Theophylline, its mechanism of action is related to the inhibition of the phosphodiesterase enzymes, but it has been claimed to have decreased affinities towards the adenosine A_1 and A_2 receptors, which has been claimed as a reason for its better safety profile [4].

The current GOLD guidelines recommend the use of Theophylline 100-600 mg once daily in COPD patients as an add-on therapy [5]. This is quite a low dose and hence, there is low chance of toxicity. Clinicians are commonly using this dose now. For Doxofylline, the commonly used dose is 400 mg B.D. So, it becomes important to compare this dose of Theophylline with Doxofylline. There are only few studies which have been done on Doxofylline 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 Doxofylline at the commonly used doses, for evaluating their efficacy and safety in patients of COPD.

SUBJECTS AND METHODS

This study was conducted in the Post-graduate Department of Pharmacology and in the Post-graduate Department of TB and Respiratory Diseases, of a medical college. It was a 3 weeks duration, randomized, prospective, parallel group and open label study. The inclusion criteria was patients (above 18 years of age) of COPD, who were diagnosed clinically and spirometrically, who had the complaints of breathlessness, tightness in the chest and cough with or without sputum. The use of Theophylline and doxophylline as single drugs was not ethical and suitable for cases of severe asthma or COPD, so only those cases having FEV_1 ranging between 60-80% were included in the study.

The Exclusion Criteria

Complicated cases of chronic obstructive pulmonary disease with respiratory failure, patients with an acute exacerbation of COPD, those with a history of myocardial infarction, patients who were on antihypertensive medication, those who were on systemic

corticosteroid and drugs which interacted with Theophylline (e.g. warfarin, digoxin), pregnant and lactating mothers and patients with clinically relevant and abnormal laboratory values which suggested an unknown disease which required further investigation were excluded from the study.

The study protocol was approved by institutional ethics committee of the medical college and an informed consent of all the patients was taken before enrolling them in the study.

The sample size was calculated from the study of Goldstein et al by using the % change in FEV_1 as a principle variable [6]. The alpha error was taken as 5% and power of 90%. The sample size came out to be 32. By adding 10% for data loss, a sample size of 35 was the minimum which was required for each group.

A total of 168 patients were enrolled, out of which 14 patients failed to report on the subsequent visits and they were excluded from the study. The remaining 154 patients were randomized into two groups at a ratio of 1:1 according to the table which was generated by the random allocation software. The patients were diagnosed as cases of COPD as per the GOLD guidelines. Group I was administered Theophylline, sustained release 400 mg once daily and group II was administered Doxofylline 400 mg twice daily, orally. No other bronchodilator was allowed as only those patients who had a mild severity (FEV_1) between 60-80% of the predicted value were included in the study.

Efficacy Assessments

The efficacies of Theophylline and Doxofylline were compared on the basis of the clinical improvement of the symptom score and the spirometric parameters before and after the drug treatment. The symptom score included shortness of breath, cough, chest tightness and night-time awakening. A graded scoring system from 0 to 5 was used.

FEV_1, FVC and the ratio of FEV_1 and FVC were recorded on days 0, 7 and 21 of the drug treatment. The pulmonary function tests were done by using SPIROLAB II (MIR). The same spirometry equipment was used throughout the study and the test was performed in accordance with a Standard Operative Procedure (SOP).

Safety Assessments

The adverse events which were experienced by the patients or which were observed by the investigator were recorded at each visit. The adverse drug reactions were assessed on a Naranjo ADR Probability Scale and also on the basis of the onset and the severity classification. A detailed physical examination which included the vital signs was performed at day 0 and at each visit. Finally, the data of the two groups were compared and analyzed by appropriate tests by using the SPSS software (version 16).

RESULTS

The 154 patients were divided into two groups. The ages of the patients ranged from 40 to 77 years. There were 120 males and 34 females. 127 patients were smokers. With respect to the smoking pattern in the pack years, 29.1% of the patients had smoked for <5 pack years, 35.43% had smoked for 5-10 pack years, and 16.53% had smoked for 10-15 pack years.

The results of this study showed that the treatment with Doxofylline 400 mg twice daily and Theophylline 400 mg SR once daily improved the spirometric variables in the COPD patients on the 7th and the 21st days of the treatment and that the improvement was statistically significant as compared to the pre-treatment values. But, the improvements in the Theophylline and the Doxofylline groups were not significantly different from each other ($p > 0.05$). The mean ± S.D. of the improvement between the two treatment groups of the patients and the p values of the different variables have been given in detail in [Table/Fig-1]. The pre- and the post-treatment values were compared by the paired t-test, whereas the Independent-Samples t-test was used to compare the means for the two groups.

The clinical improvement was calibrated on a symptom score. It was observed that there was a significant improvement in the symptom score after the drug treatment in both the groups, but these changes were not significantly different from each other ($p>0.05$) among the two groups. Being an ordinal data to compare it, the Mann-Whitney U test was applied. The comparison of the symptom scores on different days of the observation has been shown in [Table/Fig-2].

Spirometric parameter	Day of observation	Theophylline (group1) Mean ± S.D. (n =77)	Doxofylline (group 2)Mean ± S.D. (n =77)	t value	P value Sig. (2 tailed
FEV1 observed	Day 0	1.82 ± 0.34	1.81± 0.36	0.066	0.947
	Day 7	2.02 ± 0.34	2.03 ± 0.41	- 0.125	0.900
	Day 21	2.05± 0.35	2.01± 0.48	0.153	0.882
FEV1 percentage of predicted	Day 0	69.87± 4.76	69.15± 4.79	0.927	0.355
	Day 7	78.24± 5.02	77.37± 5.75	1.000	0.319
	Day 21	79.22± 4.93	78.08± 6.18	1.063	0.290
FVC observed	Day 0	2.70± 0.53	2.71 ± 0.52	0.075	0.940
	Day 7	2.74 ± 0.50	2.76 ± 0.51	-0.025	0.980
	Day 21	2.75± 0.48	2.75 ± 0.63	0.006	0.995
FVC percentage of predicted	Day 0	83.85± 6.55	83.46± 6.13	0.381	0.704
	Day 7	85.20 ± 4.91	84.81 ± 5.33	0.518	0.605
	Day 21	85.89± 5.20	85.02± 5.59	0.800	0.426
Ratio of FEV1/FVC observed	Day 0	67.19± 2.10	66.98± 2.74	0.527	0.599
	Day 7	72.25 ± 4.36	72.06 ± 3.98	0.290	0.773
	Day 21	73.18± 4.55	72.36± 4.48	0.937	0.351

[Table/Fig-1]: Comparison of improvement between Theophylline and doxophylline groups .
Values are Mean ± S. D; p < 0.05 is taken as significant. Student t-test has been applied

An assessment with respect to the heart rate and the BP was done. The results showed that the heart rate had increased in both the groups after the drug treatment, but that the increase was more in the Theophylline group as compared to that in the Doxofylline group. This was statistically significant. There was no significant effect on the blood pressure in any of the groups [Table/Fig-3]. As the data was continuous, the Independent-Samples t-test was applied to compare the pulse rate and the B.P. on different days of the observation.

The results showed that the occurrence of adverse drug reactions was not significantly different between the Theophylline and the Doxofylline groups. The adverse drug reactions were mild (no hospitalization, no change of therapy and no additional treatment) as per the severity classification in most of the cases. There was no hospitalization for the adverse drug reactions in any of the cases, while proton pump inhibiters, antiemetic and analgesics had to be prescribed for dyspepsia, nausea and headache in some cases. On the basis of the onset of adverse events, all were found to be sub-acute or latent in onset and no case was of acute onset (within 60 minutes). On the Naranjo ADR Probability Scale, the events were found to be probable in 8 cases (Score = 5-8), possible (Score = 1-4) in 17 cases and doubtful (Score = 0) in the remaining cases. Their occurrence in the groups and the comparison between them has been shown in [Table/Fig-4].

Headache was the most common side-effect which was recorded in the study. Dyspepsia or heart burn was also among the most commonly encountered side-effects in both the groups. Other notable side-effects in the Theophylline and the Doxofylline groups were nausea, vomiting and anorexia. Other category side-effects which were recorded only in the Theophylline group were diarrhoea and drug induced rash, mainly on the trunk.

DISCUSSION

The results in the patients showed that the baseline spirometric variables were similar and not statistically significant in the study groups. Active treatments resulted in improvements in the spirometric variables, which were sustained throughout the periods of the active treatment. The improvement in FEV_1 was statistically significant as compared to the value at the baseline. The improvement was statistically significant at every visit as compared to the baseline. The percent increase in the mean FEV_1 as compared to the baseline has been shown. A similar difference was observed in the FEV_1/FVC ratio.

Only few studies on Doxofylline in patients of COPD have been done and comparable studies with Theophylline are further an exceptional entity. F. Villani et al., in 1997, reported a significant improvement in FEV_1, FVC and other spirometric parameters in the β_2 responders among the COPD patients [7]. Panagia et al., in 1987 in a parallel group of 10 vs 9 patients with chronic bronchitis, compared Theophylline (200 mg t.i.d) and Doxofylline (400 mg t.i.d.) and indicated an improvement in the respiratory variables. Marino O et al., in 1988, compared Doxofylline with Theophylline SR in 25 vs 25 COPD patients and concluded that the spirometric variables had improved in both treatments.

Most of the studies had administered Theophylline in the dose of 250-400 mg twice or thrice a day, but the current recommendations for Theophylline sustained release is 100-600 mg once a day in COPD and asthma (GOLD 2007). So, in our study the dose of Theophylline sustained release was 400 mg once daily. Theophylline had no role in the acute exacerbation of COPD, but it had a role

	Observation day	Theophylline Group (n= 77)	Doxofylline group (n= 77)	P value Sig. (2-tailed)
Symptom score	Day 0	6.88 ± 3.21	6.76 ± 2.57	0.993
	Day 7	4.38± 2.38	4.33 ± 2.44	0.890
	Day 21	3.13 ± 2.02	2.84 ± 1.59	0.470

[Table/Fig-2]: Symptom score of patients on 0, 7 and 21 day of treatment Values are Mean ± S. D; p < 0.05 is taken as significant, Mann-Whitney U test has been applied.

Variables	Theophylline Group	Doxofylline Group	P value Sig. (2-tailed)
Age (in years)	46.99 ± 11.89	48.36 ± 13.25	0.458
Pulse Rate Day 0	76.86 ± 7.24	76.02 ± 6.32	0.396
Pulse Rate Day 7	81.91 ± 8.59	78.40 ± 7.42	0.003
Pulse Rate Day 21	81.97 ± 7.08	78.78 ± 7.16	0.010
B. P. Systolic Day 0	124.02 ± 6.46	125.12 ± 7.39	0.279
B.P. Systolic Day 7	124.63 ± 6.52	125.00 ± 7.54	0.722
B. P. Systolic Day 21	123.65 ± 5.85	124.69 ± 7.80	0.380
B. P. Diastolic Day 0	79.84 ± 4.45	80.27 ± 5.05	0.541
B. P. Diastolic Day 7	80.41 ± 4.78	82.47 ± 70.93	0.342
B. P. Diastolic Day 21	79.28 ± 4.79	80.09 ±4.55	0.318

[Table/Fig-3]: Effect of treatment on pulse rate & blood pressure on days of observation
Values are Mean ± S. D; p < 0.05 is taken as significant. Student t-test has been applied.

Side-effect recorded	COPD patients (n = 154)				
	Theophylline group (77)		Doxofylline group (77)		
	Number	Percentage	number	Percentage	P value
Nausea	8	10.38	6	7.79	0.298
Vomiting	4	5.19	1	1.29	0.162
Dyspepsia	11	14.28	7	9.09	0.630
Anorexia	3	3.89	3	3.89	1.000
Abdominal pain	2	2.59	0	0	0.243
Sweating	3	3.89	1	1.29	0.442
Irregular Pulse Rhythm	2	2.59	1	1.29	0.368
Palpitation	5	6.49	2	2.59	0.278
Precordial Pain	2	2.59	1	1.29	0.243
Headache	11	14.28	8	10.38	0.118
Insomnia	5	6.49	2	2.59	0.001
Anxiety/ Irritability	3	3.89	1	1.29	0.302
Seizure	0	0	0	0	
Others	4	5.19	0	0	0.266

[Table/Fig-4]: Number of subjects with adverse drug events and their comparison
p < 0.05 is taken as significant. Independent-Samples t-test has been applied.

in long-term management [8-10]. So, the sustained release tablets were considered to be clinically more relevant.

There were no significant findings in the laboratory tests and in the ECG in the Theophylline and the Doxofylline groups. The heart rate had increased in both the groups as compared to the baseline. The difference in the increase of the heart rate was more significant in

the Theophylline group than in the Doxofylline group. There were no significant changes in the systolic and diastolic blood pressures which were recorded from the baseline in both the groups on different days of the observation [Table/Fig-4].

The adverse drug reactions in both the groups were mild in severity. Cardiovascular side-effects like palpitation, an irregular pulse and precordial pain were more common in the Theophylline group but this was not statistically different (p> 0.05) as compared to the Doxofylline group. Insomnia was more common with Theophylline and it was statistically significant (p< 0.05) as compared to Doxofylline.

One of the major limitations of Theophylline is its nonselectivity for the phosphodiasterase enzyme. This was not solved by Doxofylline as well, as there is no evidence that it was a selective PDE IV inhibitor. Theophylline has an antagonistic action on the adenosine A1, A2a and A2b receptors, which is responsible for its cardiac and central nervous system stimulatory side-effects. Doxofylline has been reported to have less affinity for the adenosine receptor and it has been claimed to have a better safety profile. It has been claimed to have a decreased affinity towards the adenosine A1 and A2 receptors [4].

It is well-known that Theophylline is effective in the chronic management and the maintenance therapy of COPD. This drug can be added if the inhalational agents fail to control the disease alone, in mild cases of COPD.

Doxofylline produces an improvement in the airway obstruction as Theophylline. The data from this study showed that Doxofylline 400 mg twice a day was as effective as Theophylline 400 mg sustained release once a day in the treatment of COPD.

CONCLUSION

On the basis of the results of this study, we can conclude that the side-effects of Theophylline are not of much concern in the dose of 400 mg SR once daily and that at this dose, the side-effects are not significantly different from that of Doxofylline.

It has been recognized that Theophylline has an anti-inflammatory and an immunomodulatory effect in COPD and asthma even at low doses (plasma concentration, 5–10 mg/L) [11,12]. In COPD, low-dose Theophylline is one of the few drugs which can demonstrate clear anti-inflammatory effects and thus, it may even have a role in preventing the progression of the disease [9].

Furthermore, the reversal of the steroid resistance in COPD by Theophylline may increase the responsiveness to corticosteroids [11]. Clinical trials for exploring the interactions of Doxofylline and corticosteroids, in asthma and COPD, are the thrust areas for research and they could lead to changes in the status of xanthines in future clinical practice.

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