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Efficacy and safety of doxofylline compared to theophylline in chronic reversible asthma – a double-blind randomized placebo-controlled multicentre clinical trial

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Summary

Background:

Experimental studies have shown that doxofylline is endowed with a remarkable bronchodilator activity with less extra-respiratory effects than theophylline. This trial was designed to compare the efficacy and safety of doxofylline, theophylline, and placebo in patients with chronic reversible bronchial asthma.

Material/Methods:

Three hundred forty-six patients were randomly assigned to a 12-week oral treatment with either doxofylline 400 mg t.i.d. (high dose), doxofylline 200 mg t.i.d. (low dose), theophylline 250 mg t.i.d. (active control) or placebo. Pulmonary function tests (PFTs) were performed biweekly. Patients kept records of peak flow meter (PFM) measurements, asthma attack rate and beta-2-agonist use (albuterol).

Results:

Changes in FEV₁ 2 hours after the administration of treatments versus baseline exhibited statistically significant differences between doxofylline 400 mg t.i.d. and placebo and between theophylline and placebo. Similar differences were monitored on the other variables (FVC, PFER, FEF_{25-75%}). Asthma attack rate and use of albuterol decreased remarkably with doxofylline 400 mg t.i.d. and theophylline. There were few statistically significant differences between doxofylline 200 mg t.i.d. and placebo. Significantly more patients had to interrupt treatment because of adverse events under theophylline than under doxofylline 400 mg t.i.d. (p=0.001). With doxofylline 400 mg t.i.d., the number of patients treated to spare one drop-out due to theophylline was 5.

Conclusion:

This study provides evidence that doxofylline 400 mg t.i.d. is an effective treatment for relieving airway obstruction and displays a better safety profile with respect to theophylline 250 mg t.i.d. with a favorable risk-to-benefit ratio.

key words:

bronchial asthma • methylxanthines • theophylline • doxofylline

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BACKGROUND

Doxofylline [7-(1,3-dioxolan-2-ylmethyl) theophylline is a novel bronchodilator xanthine drug which differs from theophylline by the presence of a dioxolane group in position 7.

Bronchodilator activities of doxofylline have been demonstrated in animal studies [1–3] and in clinical trials involving patients with either bronchial asthma or chronic obstructive pulmonary disease (COPD) [4–7]. In most of the comparative studies, the efficacy of doxofylline with daily doses ranging from 200 mg to 1200 mg was found to be superior to that of placebo and similar to that of theophylline or aminophylline at dosages currently used in clinical practice [4,5,8,9].

Although it has been recognized that doxofylline shares most of the characteristics of the methylxanthine drugs, experimental studies have shown that it is associated with less extra-respiratory effects than theophylline [10–12]. It has been suggested that decreased affinities toward adenosine A₁ and A₂ receptors may account for the better safety profile of the drug [1,13,14]. Moreover, unlike theophylline, doxofylline did not antagonize calcium channel blocker receptors, nor did it interfere with the influx of calcium into the cells [15].

In asthmatic patients with concomitant duodenal ulcer treated with intravenous xanthines, a significantly less pronounced stimulation of gastric secretion was observed by Lazzaroni et al [16] following doxofylline administration. Cardiovascular tolerability of the agent has been addressed in a number of studies carried out in patients with chronic respiratory diseases. In contrast to theophylline, Dini [17] proved by 24-hour ECG Holter recording that intravenous doxofylline does not exert significant cardiac chronotropic actions. The absence of clinically important arrhythmogenic effects of the drug was also documented by other authors [8,18,19]. As shown in a recent study (different from theophylline), the use of doxofylline as a respiratory stimulant in COPD patients with nocturnal hypoxaemia was not accompanied by relevant alterations in their sleep architecture [20].

Since doxofylline was found to relieve airway obstruction similarly to theophylline but with less adverse events, the present study was designed to evaluate the efficacy and safety of orally administered doxofylline in a multicentre double-blind randomized placebo-controlled trial in patients with chronic reversible asthma using different dosages of the drug – 400 mg and 200 mg t.i.d. – compared to theophylline 250 mg t.i.d.

MATERIAL AND METHODS

Study population

This randomized, double-blind trial was carried out in United States in 22 study centers according to the Good Clinical Practice guidelines. The study population consisted of 346 adult patients with reversible obstructive

airways disease. At the screening visit, they had to have a forced expiratory volume in 1 second (FEV₁) that was within 50% to 80% of the predicted FEV₁ for their age and height, and showed at least a 15% increase in FEV₁ 30 minutes after inhalation of two puffs (180 µg) of albuterol. Patients were excluded from participation in the study in case of serious concomitant cardiovascular, renal, hepatic or metabolic diseases. Pregnant or lactating women were likewise excluded. Patients who had taken drugs known to affect theophylline clearance were also considered non-eligible.

Treatments

After written informed consent had been given, patients were randomly assigned to receive placebo, 200 mg t.i.d. doxofylline, 400 mg t.i.d. doxofylline, or 250 mg t.i.d. theophylline. The study consisted of three phases:

- 1) a 1-week, single-blind, placebo run-in phase;
- 2) a 12-week, double-blind, active-treatment phase; and
- 3) a 1-week, single-blind, placebo run-out phase.

All patients received placebo during the run-in and run-out phases. All treatments were taken orally with immediate release formulations and on a t.i.d. schedule during all three study phases. Treatments with oral xanthines, inhaled or systemic β₂-adrenergic agonists and inhaled corticosteroids were withheld between 72 hours and one week before the beginning of the study. Patients were permitted to use inhaled albuterol in case of exacerbation of asthma. The consumption of caffeine-containing beverages or chocolate was excluded for 24 hours preceding any pulmonary function test.

Study visits

Baseline pulmonary function tests (PFTs) were performed at the end of the placebo run-in phase. Patients who still had an FEV₁ that was 50% to 80% of the predicted value were given their first dose of double-blind medication, and the PFTs were repeated 2 hours later. The primary efficacy variable, which was identified in the protocol, was FEV₁. The secondary efficacy PFT variables were forced vital capacity (FVC), peak expiratory flow rate (PEFR) and forced expiration flow during the middle half of the FVC (FEF_{25%-75%}). All PFTs in the study were performed in triplicate, and the best of the three was recorded.

Patients returned for subsequent PFTs at 14-day intervals during the active-treatment period and the end of the placebo run-out period. At each visit, PFTs were measured before the first dose of the day was taken and 2 hours after dose administration, providing at least 8 hours had elapsed between the first PFT measurement and the last use of albuterol.

At each visit, the patients were given a diary card, a peak flow meter (PFM) and albuterol inhalers. The patients used the diary cards to record date and time

each dose of study medication was taken, date and time of asthmatic episodes, date and time of each albuterol aerosol use, PFM measurements and date and time of adverse events. The recordings of PFM were performed by the patient each morning before the first dose of the medication was taken. Albuterol inhalers could be used at any time throughout the study for relief of acute asthma symptoms. A 12-lead ECG tracing was performed at the screening visit and at the end of double-blind treatments.

All clinical adverse events were recorded and graded as mild, moderate or severe. Their relationships with active treatments were classified as follows: 1) not related, 2) possibly related, 3) definitely related or 4) unknown. Also recorded for each event were the duration of the symptoms and the action taken (none, reduction of the dose or discontinuation of treatment). Removal of subject from therapy or assessment was determined by: 1) persistent drug-related adverse event with patient's willingness to discontinue treatment, 2) serum theophylline levels exceeding 20 µg/mL or 3) elevated doxofylline concentrations (>2 standard deviations of means [SD]) in the presence of any drug-related adverse event.

Drugs and laboratory analyses

Blood samples for drug concentration measurements were drawn immediately before all PFTs after 5, 9, and 13 weeks of active treatment. Hematology, blood chemistry and urinalysis were performed at the screening visit and after 3 and 13 weeks.

Statistical analysis

The study sample was estimated to be 50 subjects in each group based on FEV₁, after having considered: 1) a standard deviation of 7%, and 2) identified the minimal difference of clinical significance with a power of 95%, a β error of 0.05 and an α error of 0.05 [21].

Data are expressed as mean ± standard error of means (SEM). The statistical analysis compared the results of the PFTs obtained at baseline (immediately prior to the start of double-blind treatment) with the results

obtained 2 hours after administration of study medication at each visit during double-blind treatment. The derived variable was the percent change between these two assessments. Absolute changes were calculated for the asthmatic attack rate (total number of attacks divided by total number of days on study medication) and albuterol use rate (total number of puffs divided by total number of days on study medication). Baseline for the latter two variables was defined as the value obtained from the diaries during the placebo run-in phase. A two-way analysis of variance was used for analysis of all efficacy variables.

Two-way analysis of variance with covariates, descriptive statistics and the Wilcoxon model was utilized to examine non-parametric variables. Serum doxofylline levels from patients in the doxofylline group were analyzed for a possible relationship between serum levels and FEV₁ response using the correlation analysis approach. Differences were considered significant at the p<0.05 level.

RESULTS

Study groups

The mean age of the study population was 35.5±17.0 years. The percent of women was 51%. Races of the study population included caucasian (n=289), black (n=19), hispanic (n=32) and mongolian (n=6). Of the study patients, 88 were assigned to doxofylline 400 mg t.i.d., 86 to theophylline 250 mg t.i.d., 83 to doxofylline 200 mg t.i.d., and 89 to the placebo group. The four treatment groups were comparable at baseline with respect to demographics, history of asthma and precipitating factors (Table 1). A majority of the subjects received one or more concomitant medications. Of note, 24% in the doxofylline 200 mg t.i.d. group, 16% in the doxofylline 400 mg t.i.d. group, 9% in the theophylline 250 mg t.i.d. group and 18% in the placebo group received oral treatment with corticosteroids.

Pulmonary function tests

Baseline efficacy variables were similar and not statistically different in the study groups (Table 2). Active

Table 1. Characteristics of the study patients.

Characteristic	Doxo 200 mg t.i.d.	Doxo 400 mg t.i.d.	Theo 250 mg t.i.d.	Placebo
N	83	88	86	89
Sex (M/F)	44/39	44/44	38/48	44/45
Mean age (yr)	33.0	36.6	36.0	36.4
Mean weight (kg)	79.1	78.9	78.8	83.0
Mean height (cm)	171.1	169.7	168.0	171.8
Mean % of predicted FEV ₁	66.2	64.5	66.4	64.9
Precipitating factors	98.8%	97.7%	96.5%	96.6%
Hospitalizations for asthma	38.6%	42.0%	41.9%	37.1%
Mean age at asthma onset (yrs)	13.9	16.1	16.8	18.0
Mean years since onset	19.0	20.2	19.2	18.4

Legend: Doxo: doxofylline, Theo: theophylline.

CR

Table 2. Baseline efficacy variables.

Variable	Doxo 200 mg t.i.d.(N=83)	Doxo 400 mg t.i.d.(N=88)	Theo 250 mg t.i.d.(N=86)	Placebo(N=89)
FEV ₁ (L)	2.49±0.08	2.29±0.06	2.36±0.07	2.37±0.07
FVC (L)	3.55±0.11	3.28±0.10	3.40±0.12	3.41±0.11
PEFR (L/sec)	6.07±0.22	5.59±0.20	5.87±0.22	5.93±0.24
FEF _{25-75%} (L/sec)	2.01±0.11	1.85±0.12	1.92±0.11	1.88±0.09
Asthma attacks (no./day)	1.84±0.20	1.94±0.18	1.72±0.20	1.77±0.21
Albuterol use (puffs/day)	3.59±0.40	3.73±0.34	3.31±0.38	3.40±0.48

Doxo: doxofylline, Theo: theophylline.

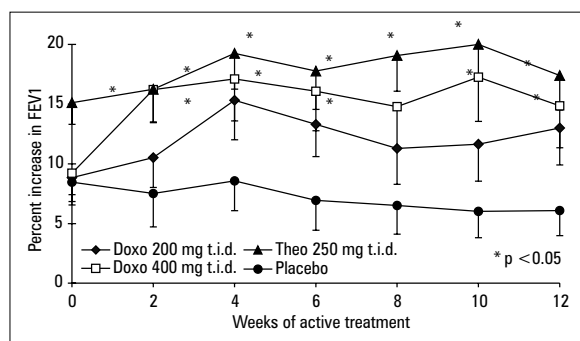


Figure 1. Mean percent increase in FEV₁ two hours after the administration of active treatments or placebo during the 12-week of active treatment. Differences from placebo were significant for doxofylline 400 mg t.i.d. and theophylline 250 mg t.i.d. ($p < 0.05$) at every visit, except week 0 and 8 for doxofylline 400 mg t.i.d. T-bars represent SEM.

treatments resulted in improvements in primary and secondary PFT variables that were sustained throughout the period of active treatment. There were statistically significant differences between doxofylline 400 mg t.i.d. and placebo and between theophylline and placebo for FEV₁. The percent increases in mean FEV₁ during double-blind therapy are displayed in Figure 1.

Similar differences were monitored on the other variables (FVC, PEFR and FEF_{25%-75%}). Mean FVC increase over placebo was significant at every visit except week 0 and 4 for the doxofylline (400 mg t.i.d.) group ($p < 0.05$), while statistical significance with theophylline was not accomplished at week 0, 2, 6 and 10. Mean PEFR increase over placebo was statistically significant at week 10 and 12 in the doxofylline 400 mg t.i.d. group and at week 4 and 8 through the end of the study for the theophylline group. The change in FEF_{25%-75%} was significantly different from placebo ($p < 0.05$) at week 2, 4, 8, 10 for the doxofylline 400 mg t.i.d. group and at every visit except week 6 for the theophylline group.

Peak flow meter measurements

There were sustained increases in the average daily peak flow meter rate in both doxofylline 400 mg t.i.d. and theophylline groups. The differences between doxofylline 400 mg t.i.d. and placebo were statistically significant at week 2 and 6 ($p < 0.05$). The differences

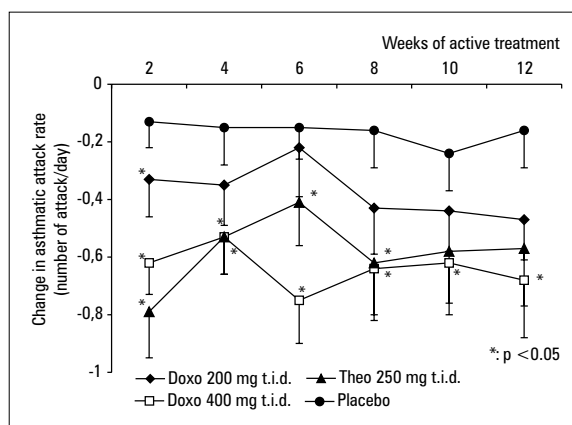


Figure 2A. Mean decrease of number of daily asthma attacks during double-blind treatment. The differences between doxofylline 400 mg t.i.d. and placebo were significant ($p < 0.05$) at every visit, while the differences between theophylline and placebo were significant ($p < 0.05$) at week 2 through 8. T-bars represent SEM.

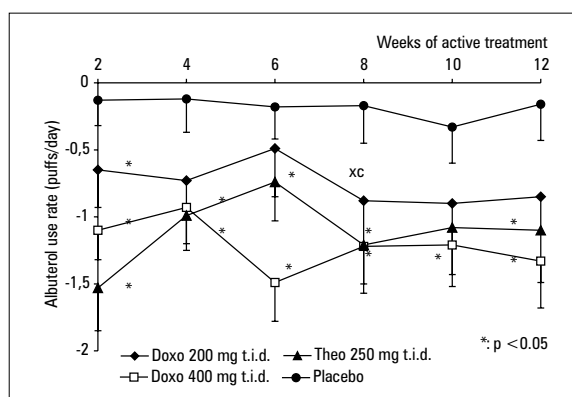


Figure 2B. Mean decrease of number of daily albuterol puffs during double-blind treatment. The differences from doxofylline 400 mg t.i.d. compared to placebo were statistically significant ($p < 0.05$) at every evaluation during active treatment. For the theophylline group, the differences from placebo were statistically significant at every visit except week 10. T-bars represent SEM.

between theophylline and placebo were statistically significant at week 2 and 12 ($p < 0.05$).

Asthmatic attacks and beta-2 agonist consumption

There was a decrease in the average asthma attack rate in all treatment groups at every evaluation during the study. Both doxofylline 400 mg t.i.d. and theophylline 250 mg t.i.d. were particularly effective in reducing the asthma attack rate (Fig. 2A). There was only one significant difference (week 2) between doxofylline 200 mg t.i.d. and placebo.

The decreases in asthma attack rate were accompanied by statistically significant decreases in the use of albuterol to relieve asthmatic symptoms in patients receiving active treatments (Fig. 2B). The differences from placebo were statistically significant ($p < 0.05$) at every visit with doxofylline 400 mg t.i.d. For the theophylline group, the differences from placebo were statistically significant at every visit but week 10. With doxofylline 200 mg, statistical significance over placebo ($p < 0.05$) was obtained only at week 2.

Safety

Forty-three patients dropped-out because of occurrence of criteria for interruption: 31.4% in the theophylline group, 11.4% in the doxofylline 400 mg t.i.d. group, 3.6% in the doxofylline 200 mg t.i.d. group and 3.4% in the placebo group (Fig. 3). In the theophylline group, 15 were withdrawn because of adverse events, 8 because of adverse events plus a theophylline level above 20 µg/mL and 4 patients were withdrawn solely because their theophylline levels were above 20 µg/mL. Of the 9 patients that were withdrawn from the study because of adverse events in the doxofylline 400 mg t.i.d. group, 3 had drug serum levels >2 SD. Statistical significant differences were reached either with theophylline and doxofylline groups, theophylline and placebo or doxofylline 400 mg

and placebo. More interestingly, significantly more patients had to interrupt the treatment because of adverse events (or drug concentrations above the upper limit of normality) under theophylline than under doxofylline 400 mg t.i.d. ($p = 0.01$). The number needed to treat to spare one treatment interruption was 5.

Adverse events were reported in 180 of the study patients (Table 3). They occurred more frequently with theophylline (63%) than with doxofylline 400 mg t.i.d. (52%), doxofylline 200 mg t.i.d. (49%) or placebo (44%). The most common adverse event was headache, which took place in about the same proportion of patients in all treatment groups (27–29%). There was a trend towards a more frequent occurrence of nausea in the theophylline group (33%) than with doxofylline 400 mg t.i.d. (16%) or placebo (19%). Dyspepsia, insomnia and nervousness, also occurred more often with theo-

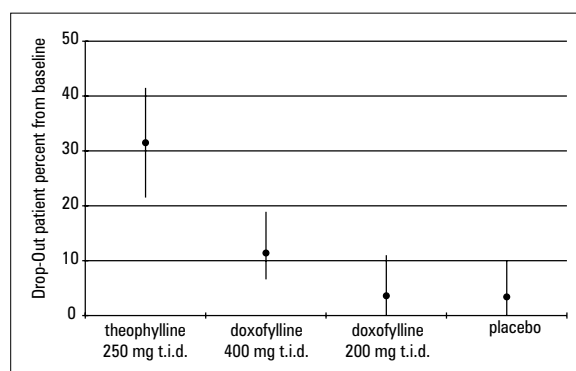


Figure 3. Proportion ($\pm 95\%$ confidence interval) of subjects who interrupted treatment due to adverse events (or to drug concentrations above the upper limit of normality) in the study groups.

Table 3. Number of subjects in each group with drug-related adverse events.

Event	Doxo 200 mg t.i.d. (N=83)	Doxo 400 mg t.i.d. (N=88)	Theo 250 mg t.i.d. (N=86)	Placebo (N=89)
Headache	2	3	4	2
Nausea		1	3	1
Nervousness	1	3	1	
Insomnia	1	1	2	
Asthma		1		1
Anxiety	1		1	
Dizziness		1	1	
Palpitations		1	1	
Dyspepsia			1	
Chest pain		1		1
Thinking abnormal		1	1	
Tremor		1	1	
Overdose			1	
Abdominal pain			1	
Vasodilatation				
Gastritis				
No drug effect				1
Dyspnea				1
Lung function decreased				1

An adverse event was considered drug related if the investigator rated the relation to study medication as "possible", "definite" or "unknown".

Table 4. Percent increase in FEV₁ and serum doxofylline levels during double-blind therapy.

	week 5	week 9	week 13
Doxo 200 mg t.i.d.			
N	68	66	60
Change in FEV ₁ (%)	11.1	12.6	11
Serum level (µg/mL)	4.2	3.7	3.2
Doxo 400 mg t.i.d.			
N	69	59	53
Change in FEV ₁ (%)	16.8	16.2	17.2
Serum level (µg/mL)	12.7	13.7	12.5
Theo 250 mg t.i.d.			
N	55	23	31
Change in FEV ₁ (%)	16.2	17.6	19.7
Serum level (µg/mL)	10.8	11.8	11.2

phylline compared with either the doxofylline groups or placebo.

There were no clinical significant effects on laboratory test results, ECG or physical examination. On vital signs, heart rate increased in average by 2–5 bpm with theophylline, whereas it remained unchanged or slightly decreased during doxofylline treatment. Palpitations and tachycardia occurred more frequently with theophylline (7%) than with doxofylline 400 mg (5%), doxofylline 200 mg (1%) or placebo (none).

Drug concentration measurements

The mean serum concentrations of doxofylline 400 mg t.i.d. were 12.7±4.3 µg/mL, 13.7±4.1 µg/mL and 12.5±3.9 µg/mL after 5, 9 and 13 weeks, respectively. At the end of the same periods, they were 4.2±3.5 µg/mL, 3.7±3.9 µg/mL and 3.2±2.8 µg/mL for doxofylline 200 mg t.i.d. In patients receiving theophylline 250 mg t.i.d., the mean serum concentration of drug were 10.8±4.9 µg/mL, 11.8±5.3 µg/mL and 11.2±5.0 µg/mL. Elevations in serum theophylline levels exceeding the upper limit of normality were observed in 12 patients. The comparative values of the changes in FEV₁ at visits 5, 9 and 13 and the corresponding serum levels of xanthines are displayed in Table 4.

DISCUSSION

The results of the study demonstrated the efficacy and the tolerability of doxofylline in the management of patients with chronic reversible asthma in a double-blind randomized placebo-controlled clinical trial. Both doxofylline 400 mg t.i.d. and theophylline 250 mg t.i.d. significantly improved spirometric variables. Particularly, significant improvement over placebo was observed on FEV₁ with doxofylline 400 mg t.i.d. (+14.9%) and theophylline 250 mg t.i.d. (+17.4%) at the end of the 12-week active treatment period.

Our results are consistent with those of previous studies that assessed the effects of orally administered doxofylline in the management of patients with chronic res-

piratory diseases [4–7,22]. Melillo et al [22] examined the clinical effects of doxofylline in 139 patients with asthma treated in a double-blind randomized fashion with either doxofylline 400 mg b.i.d. or theophylline 300 mg slow-release b.i.d. Both doxofylline and theophylline treatments significantly improved all pulmonary function parameters as compared to baseline ($p < 0.05$), but were not statistically different from each other. Specifically, the percent changes in FEV₁ at after 28-day treatment was +13.8% with doxofylline and +16.1% with theophylline.

In the present study, oral treatment with doxofylline was effective in relieving airway obstruction of patients with chronic reversible asthma. Whereas theophylline brought about improvements in FEV₁ after the first dose, doxofylline was associated with marked increases in the bronchodilator response after the first week of treatment (Figure 1). Doxofylline 400 mg was particularly efficacious in decreasing the asthma attack rate and/or the need for rescue albuterol inhalation. Since subjective benefits do not always correlated closely to PFT changes, the ability of doxofylline to reduce the frequencies of asthma exacerbation episodes and β_2 -agonist consumption appears to be particularly advantageous in patients with bronchial airway obstruction [23]. Even if not statistically significant, low dose doxofylline elicited improvement in FEV₁ after 12-week treatment period (+13%). The variability of the bronchodilatory responsiveness may partly account for the absence of statistical significance in the group given doxofylline 200 mg t.i.d.

Adverse events occurred in a greater proportion of patients in the theophylline group and a higher number of patients were withdrawn because of adverse events. Although the number of adverse events in the study population was rather elevated, their frequency was similar to that of previous comparative studies of xanthine medications in asthmatic patients [24,25]. Furthermore, the percentage of adverse events in the doxofylline 400 mg t.i.d. group exceeded slightly that of the placebo, while their frequency in the doxofylline 200 mg group was comparable with that of the placebo group. Inclusion of the 400 mg t.i.d. dose of doxofylline in our study was done specifically to allow us to compare the tolerability of the highest recommended dose to that of the standard recommended dose of 400 mg b.i.d. of doxofylline. The results showed that, even at this maximum dosage, doxofylline was better tolerated than theophylline. Indeed, there was one adverse event spared by doxofylline 400 mg t.i.d. for every 5 patients treated with theophylline.

Headache was the most commonly reported adverse event in the overall study population. In accordance with previous studies [22,26], gastro-intestinal adverse events were more common with theophylline than with doxofylline. While palpitations or tachycardia occurred similarly in both doxofylline and theophylline treatment groups, these events led to discontinuation more often with theophylline than with doxofylline.

It is well known that the concentration of theophylline in the blood is directly related to bronchodilator response, but may easily produce toxic levels in both asthmatic and COPD patients [27]. With either doxofylline 200 mg t.i.d. or doxofylline 400 mg t.i.d., serum doxofylline levels were found stable throughout the study (Table 4). No evidence of an association between serum doxofylline levels and the occurrence of adverse events was noted. Finally, neither doxofylline nor theophylline had any apparent effect on other laboratory test results.

There are several limitations to this study especially as concerns the theophylline treatment group. A single dosing schedule of theophylline was used without attempts made at dose adjustment based on theophylline level and/or toxicity. Patients with levels greater than or equal to 20 mcg/ml with or without symptoms were dropped from the study. Adjusting doses may have led to less toxicity and fewer withdrawals from the theophylline treatment group. If more frequent theophylline levels had been drawn with dose adjustment, this might have led to less theophylline toxicity and a smaller number of dropouts. However, our intent was to compare a single dosing schedule of theophylline with two different single dosing schedules of doxofylline – therefore precluding dose adjustments.

CONCLUSIONS

In conclusion, the data from this double-blind placebo-controlled study showed that doxofylline 400 mg t.i.d. is as effective as theophylline 250 mg t.i.d. in the treatment of chronic reversible asthma. Doxofylline has exhibited 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 asthma attacks. Second, it has a favorable tolerability profile that suggests that this drug might be of particular benefit in selected groups of asthmatic patients, especially those with gastrointestinal intolerance to theophylline. Since doxofylline 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 chronic management of patients with chronic reversible asthma.

Appendix

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REFERENCES

1. Franzone JS, Cirillo R, Barone D: Doxofylline and theophylline are xanthines with partly different mechanisms of action in animals. *Drug Exptl Clin Res*, 1988; 14: 479-489
2. Franzone JS, Cirillo R, Biffignandi P: Doxofylline exerts a prophylactic effects against bronchoconstriction and pleurisy induced by PAF. *Eur J Pharmacol*, 1989; 165: 269-277
3. Sugeta A, Imai T, Idaira K et al: Effects of theophylline and doxofylline on airway responsiveness in beagles. *Arerugi*, 1997; 46: 7-15
4. Bucca C, Rolla G, Fonzo D et al: Acute clinical-pharmacological findings in obstructive pneumopathy following 2(7, -theophyllin-methyl)1, 3-dioxolane (doxofylline). *Int J Clin Pharm Res*, 1982; 4: 101-103
5. Dolcetti A, Osella D, De Filippis G et al: Comparison of intravenously administered doxofylline and placebo for the treatment of severe airways obstruction. *J Int Med Res*, 1988; 16: 264-269
6. Poggi R, Brandolese R, Bernasconi M et al: Doxofylline and respiratory mechanics. Short-term effects in mechanically ventilated patients with airflow obstruction and respiratory failure. *Chest*, 1989; 96: 772-778
7. Villani F, De Maria P, Ronchi E et al: Oral doxofylline in patients with chronic obstructive pulmonary disease. *Int J Clin Pharmacol Ther*, 1997; 35: 107-111
8. Checchini M, Magni M, Scaglione M et al: Studio clinico controllato doxofyllina versus aminofyllina nel trattamento delle sindromi da insufficienza acuta cardiorespiratoria. *Minerva Cardioangiol*, 1997; 45: 185-190
9. Dini FL, Pasini G, Cortellini G et al: Methylxanthine drug therapy in chronic heart failure associated with hypoxaemia: double-blind placebo controlled clinical trial of doxofylline versus theophylline and bamifylline. *Int J Clin Pharm Res*, 1993; 13: 305-316
10. Cravanzola C, Reboani MC, Grosa G et al: Doxofylline in rat brain in relation to locomotor activity. *Drug Metab Dispos*, 1989; 17: 437-440
11. Cirillo R, Grossi E, Franzone JS: Doxofylline, an adenosine non-blocking xanthine, does not induce cardiostimulants effects. *Res Com Chem Path Pharmacol*, 1989; 65: 21-34
12. De Sarro A, Grasso S, Zappala M et al: Convulsant effects of some xanthine derivatives in genetically epilepsy-prone rats. *Naunyn Schmiedebergs Arch Pharmacol*, 1997; 356: 48-55
13. Cirillo R, Barone D, Franzone JS: Doxofylline, an antiasthmatic drug lacking affinity for adenosine receptors. *Arch Int Pharmacodyn*, 1988; 295: 221-237
14. Barnes PJ, Pauwels RA: Theophylline in the management of asthma: time for reappraisal? *Eur Respir J*, 1994; 7: 579-591
15. Franzone JS, Cirillo R, Reboani MC: Doxofylline differs from methylxanthines in its movement of cytosolic calcium. *Int J Tiss React*, 1991; 18: 131-138
16. Lazzaroni M, Grossi E, Banchi Porro G: The effect of intravenous doxofylline or aminophylline on gastric secretion in duodenal ulcer patients. *Aliment Pharmacol Therap*, 1990; 4: 643-649
17. Dini FL: Chronotropic and arrhythmogenic effects of two methylxanthine bronchodilators, doxofylline and theophylline, evaluated by Holter monitoring. *Curr Ther Res*, 1991; 49: 978-984
18. Cipri A, Pozzar F, Dini FL: Alterazioni del ritmo cardiaco in pazienti con broncopneumopatia cronica ostruttiva. *Minerva Cardioangiol*, 1992; 40: 31-39
19. Dini FL, Cogo R: Doxofylline, a new xanthine bronchodilator devoid of major cardiovascular adverse effects. *Curr Med Res & Opin*, 2001; 16: 258-268
20. Sacco C, Braghiroli A, Grossi E et al: The effects of doxofylline versus theophylline on sleep architecture in COPD patients. *Monaldi Arch Chest Dis*, 1995; 50: 98-103
21. Altman DG: Statistics and ethics in medical research. III. How large a sample? *Br Med J*, 1980; 281: 1336-1338
22. Melillo G, Balzano G, Jodice F et al: Treatment of reversible chronic airways obstruction with doxofylline compared with slow-release theophylline: a double-blind, randomized, multicentre trial. *Int J Clin Pharm Res*, 1989; 9: 397-405

-
23. Rees PJ: Bronchodilators in the therapy of chronic obstructive pulmonary disease. In: Postma DS, Siafakas NM (eds). Management of chronic obstructive pulmonary disease. The European Respiratory Monograph, 1998; 7: 135-149
 24. Dini FL: Metilxantine e sistema cuore-polmoni. Passato, presente e futuro. C.G. Edizioni Medico-Scientifiche, Torino, 1993: pp 23-30
 25. Chapman KR, Ljungholm K, Kallen A: Long-term xanthine therapy of asthma. Enprofylline and theophylline compared. International Enprofylline Study Group. Chest, 1994; 106: 1407-1413
 26. Grossi E, Biffignandi P, Franzone JS: La doxofilina: profilo del farmaco e rassegna degli studi clinici. Eur Rev Med & Pharmacol Sci, 1988; 10: 1-16
 27. Bierman CW, Williams PV: Therapeutic monitoring of theophylline: rationale and current status. Clin Pharmacokinetic, 1989; 17: 377-384

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