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Impact of doxofylline compared to theophylline in asthma: a pooled analysis of functional and clinical outcomes from two multicentre, double-blind, randomised studies (DOROTHEO 1 and DOROTHEO 2)

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Abstract

This pooled analysis of double-blind, randomized, placebo-controlled trials aimed to investigate the Impact of DOxofylline compaRed tO THEOphylline (DOROTHEO 1 and DOROTHEO 2 studies) on functional and clinical outcomes in asthma. Patients with asthma ≥16 years of age with (forced expiratory volume in 1 s [FEV₁] ≥50% and <80% and with ≥15% post-bronchodilator increase in FEV₁) were randomized in a 1:1:1:1 ratio in DOROTHEO 1 to receive doxofylline 200 mg, doxofylline 400 mg, theophylline 250 mg, or placebo; in DOROTHEO 2 patients were randomized in a 1:1:1 ratio to receive doxofylline 400 mg, theophylline 250 mg, or placebo. All double-blind treatments were taken orally with immediate release formulations and three times daily. Data evaluating the effect of doxofylline 400 mg, theophylline 250 mg and placebo on FEV₁, asthma events rate, use of salbutamol as rescue medication and adverse events (AEs) were pooled from both studies. The pooled-analysis of 483 patients demonstrated that both doxofylline 400 mg and theophylline 250 mg significantly increased FEV₁, reduced the rate of asthma events and use of salbutamol to relieve asthma symptoms compared to placebo (p<0.01). No significant differences were detected between doxofylline 400 mg and theophylline 250 mg. Doxofylline 400 mg did not significantly (p>0.05) increase the risk of AEs compared to placebo, conversely in patients treated with theophylline 250 mg the risk of AEs was significantly (p<0.05) greater than in those that received placebo. We conclude that doxofylline seems to offer a promising alternative to theophylline with a superior efficacy/safety profile in the management of patients with asthma.

Keywords

Asthma, doxofylline, theophylline, pooled analysis.
1. Introduction

Xanthines are structurally related drugs, used in clinical management of patients with chronic obstructive respiratory disorders, including asthma and chronic obstructive pulmonary disease (COPD). However, commonly used xanthines (theophylline, aminophylline) have a major drawback in that they have a very narrow therapeutic window and propensity for many pharmacological interactions [1-6]. The advent of other classes of drugs, such as the new inhaled corticosteroids (ICSs) and long-acting bronchodilator agents, has limited the use of xanthines, despite their clear clinical benefit in the treatment of some patients with chronic obstructive respiratory disorders [3].

Doxofylline is a newer generation xanthine with bronchodilating and anti-inflammatory actions [7-11]. In experimental animals, this drug has also been shown to have anti-inflammatory activity in a rat pleurisy model and to inhibit human eosinophil activation by affecting Ca\(^{2+}\) activated K\(^+\) channels [12, 13]. Doxofylline is also able to provide prophylactic effects against bronchoconstriction induced by platelet-activating factor and methacholine in guinea-pigs and dogs [13-15].

In human, two multicenter, double-blind, randomized trials, carried out in 21 Italian pulmonary clinics to investigate the therapeutic efficacy and tolerability of doxofylline compared to slow-release theophylline or aminophylline, demonstrated that doxofylline is an effective and well tolerated agent in patients suffering from chronic reversible airways obstruction [16, 17]. A number of other studies confirmed the beneficial clinical effects of doxofylline in asthma and COPD [1, 5, 18].

In summary, bronchodilatory effects of doxofylline have been demonstrated in patients suffering from asthma or COPD [1, 2, 15, 19-21], but, to the best of our knowledge, large scale data comparing the efficacy and safety of doxofylline to those of the more commonly used theophylline in the treatment of asthma are still lacking. To explore this, we examined data from two independent, double-blind, randomized, placebo-controlled trials that aimed to
investigate the Impact of DOxofylline compaRed tO THEOphylline (DOROTHEO 1 and DOROTHEO 2 studies) [22, 23] in asthma. Data were pooled in order to perform a pre-specified analysis of the two studies, which together are powered to provide more reliable estimates of the effect of the investigated drugs on lung function, asthma events rate, use of salbutamol to relieve asthma symptoms, and adverse events (AEs).

2. Materials and methods

2.1. Study design

DOROTHEO 1 and DOROTHEO 2 were Phase III, multicentre, double-blind, randomized, parallel-group, placebo-controlled, clinical trials, conducted in 37 centres in the United States [22, 23]. Each study had one week run-in period during which the subject took placebo followed by 12-week treatment period and a 1-week single-blind placebo run-out phase at the end of the study. Patients were randomized in a 1:1:1:1 ratio in DOROTHEO 1 to receive doxofylline 200 mg, doxofylline 400 mg, theophylline 250 mg, or placebo. Patients were randomized in a 1:1:1 ratio in DOROTHEO 2 to receive doxofylline 400 mg, theophylline 250 mg, or placebo. All treatments were taken orally with immediate release formulations and three times daily (tid) during all the study phases.

The studies were conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation/Good Clinical Practice Guidelines and local regulations. The study protocols were reviewed and approved by Institutional Review Boards at each study centre. The studies have been registered in the International Standard Randomised Controlled Trial Number (ISRCTN65297911 and ISRCTN22374987) and detailed information can be found at http://www.isrctn.com/ISRCTN65297911 and http://www.isrctn.com/ISRCTN22374987.

2.2. Study population
Patients with asthma who were ≥16 years old, who had forced expiratory volume in 1 s (FEV₁) within 50% to 80% of the predicted and who showed at least 15% post-bronchodilator (salbutamol 180 µg) increase in FEV₁ were enrolled. Key exclusion criteria included 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 excluded. The study flowchart is reported in supplementary data file (Table S1).

Patients were permitted to use inhaled salbutamol as rescue medication. Treatments with other oral xanthines, inhaled β₂-agonists or antimuscarinic agents and inhaled corticosteroids were withheld between 72 hours and one week before the beginning of the study and during the study period.

2.3. Study endpoints

The primary endpoint of this pooled analysis was the change from baseline in FEV₁, expressed as percentage (%), after 12 weeks of treatment.

The secondary endpoints included: i) the overall change from baseline in FEV₁ during the study period vs. placebo and between active treatments; ii) the change from baseline in asthma events rate (n/day) after 12 weeks of treatment and the overall change during the study period vs. placebo between active treatments; and iii) the change from baseline in salbutamol use rate (puffs/day) after 12 weeks of treatment and the overall change during the study period vs. placebo between active treatments.

This pooled analysis assessed the effect of doxofylline 400 mg, theophylline 250 mg, or placebo in asthmatic patients. The effect of doxofylline 200 mg was investigated only in DOROTHEO 1 [22] and therefore was not included in this pooled analysis.

The patients used diary cards to record the date and time that each dose of study medication was taken, date and time of asthma episodes, date and time of each salbutamol use, and date and time of any AEs.

2.4. Assessment of safety and drop-outs
All clinical AEs 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). Subjects were removed from therapy or assessment for: 1) non-adherence to treatment, 2) persistent drug-related AEs with patient’s willingness to discontinue treatment, 3) serum theophylline levels exceeding 20 µg/mL or 4) elevated doxofylline concentrations (>2 standard deviations above the mean) in the presence of any drug-related AE.

2.5. Statistical analysis

Data are expressed as mean ± standard error of the mean (SEM). The statistical analysis compared FEV\textsubscript{1} measured by spirometry obtained at baseline (immediately prior to the start of double-blind treatment) with the results obtained 2 hours after administration of study medication (2-h postdose FEV\textsubscript{1}) at each visit during double-blind treatment. The derived variable was the percent change between these two assessments. Absolute changes were calculated for the asthma events rate (total number of events divided by total number of days on study medication) and salbutamol 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. The safety analysis was performed by calculating the risk of AEs compared to placebo, and data were reported as risk ratio (RR) and 95% confidence interval (95%CI).

The DOROTHEO 1 and DOROTHEO 2 studies [22, 23] had similar protocol, with the same treatment groups, except that DOROTHEO 1 included also a low dose doxofylline group (200 mg tid).

The analysis of the changes from baseline was performed by using \( t \)-test, whereas the two-way analysis of variance (ANOVA) was used for evaluating the difference across the treatments during the study period. All differences were considered significant for \( P<0.05 \). Data analysis was performed by using
Prism 5 software (GraphPad Software Inc, CA, USA) and OpenEpi software [24].

3. Results

3.1. Patient population

Six hundred sixty six patients were screened for participation in the pooled studies [22, 23] and entered the placebo wash-out. One hundred patients did not enter the double-blind period because they either no longer met all the selection criteria. A total of 566 patients were enrolled and randomized. Of the patients randomized, 63 received doxofylline 200 mg, 163 received doxofylline 400 mg, 155 were treated with theophylline 250 mg and 165 were administered placebo during a period of treatment of 12 weeks. Data for the doxofylline 200 mg are not reported in this pooled analysis because it was investigated only in DOROTHEO 1 study [22]. Patient enrolment and the reasons for discontinuation are presented by treatment group in Figure 1.

Figure 1. CONSORT diagram of patient flow in the pooled DOROTHEO 1 and DOROTHEO 2 studies. Data for the doxofylline 200 mg are not reported in this pooled analysis and can be found elsewhere [22].
Patient demographics and baseline characteristics were similar with no significant differences (P>0.05) across the treatment groups, as reported in Table 1. The summary of prior asthma medications is reported in is reported in supplementary data file (Table S2).

**Table 1.** Patient demographics and baseline characteristics for the pooled DOROTHEO 1 and DOROTHEO 2 studies.

|                         | Doxofylline 400 mg (n=163) | Theophylline 250 mg (n=155) | Placebo (n=165) |
|-------------------------|-----------------------------|----------------------------|-----------------|
| Age (years, mean±SEM)   | 36.23±1.35                  | 36.31±1.5                  | 36.95±1.55      |
| Gender (male, n and %)  | 79 (48.47)                  | 70 (45.16)                 | 75 (45.45)      |
| Ethnicity (n and %)     |                             |                            |                 |
| Caucasians              | 139 (85.28)                 | 131 (84.52)                | 145 (87.88)     |
| African Americans       | 10 (6.13)                   | 12 (7.74)                  | 9 (5.45)        |
| Latin Americans         | 10 (6.13)                   | 12 (7.74)                  | 9 (5.45)        |
| Others                  | 4 (2.45)                    | 0                          | 1 (0.61)        |
| Body Weight (kg, mean±SEM) | 79.52±2.13                  | 79.91±2.04                 | 80.55±1.91      |
| Height (cm mean±SEM)    | 168.08±1.42                 | 167.55±1.70                | 168.70±1.58     |
| FEV₁ (L, mean±SEM)      | 2.29±0.06                   | 2.36±0.07                  | 2.34±0.07       |
| FEV₁ (% predicted, mean±SEM) | 64.92±1.15                 | 66.58±1.15                 | 65.92±1.02      |
| Asthma events (n/day, mean±SEM) | 1.88±0.17             | 1.77±0.18                  | 1.77±0.19      |
| Salbutamol use (puffs/day, mean±SEM) | 3.63±0.34          | 3.41±0.35                  | 3.45±0.43      |
| Precipitating factors (n and %) | 160 (98.16)               | 150 (96.77)                | 156 (94.55)    |
| At least one past hospitalization for asthma (n and %) | 71 (43.56) | 64 (41.29) | 64 (38.79) |
| Age at onset of asthma (years, mean±SEM) | 15.00±1.50 | 15.69±1.66 | 17.95±1.80 |
| Duration of asthma (years, mean±SEM) | 21.12±1.45 | 20.62±1.49 | 19.00±1.50 |

**3.2. Lung function (FEV₁)**

Both doxofylline 400 mg and theophylline 250 mg significantly (P<0.001) increased 2-h postdose FEV₁ compared to baseline after 12 weeks of treatment (+16.32±3.29% and +15.73±3.37%, respectively), and these improvements exceeded the minimum clinically important difference (MCID) of 12% and 200 mL (+374±75 mL and +371±80 mL, respectively) [25, 26].
Additionally, both doxofylline 400 mg and theophylline 250 mg significantly (p<0.001) improved the change from baseline in 2-h postdose FEV₁ vs. placebo during the study period (Figure 2). No significant (P<0.05) difference were detected between doxofylline 400 mg and theophylline 250 mg with respect to 2-h postdose FEV₁ from week 2 onwards (absolute difference: 1.42±3.08%).

**Figure 2.** Impact of doxofylline 400 mg, theophylline 250 mg and placebo on the change from baseline in 2-h postdose FEV₁ (A: %; B: mL), as measured during clinic visits. The MCID reported as 12% change in FEV₁ on the y axis (A) corresponds to 278 mL change in FEV₁ by considering the asthmatic patients enrolled in DOROTHEO 1 and DOROTHEO 2 studies.
FEV₁: forced expiratory volume in 1 s; MCID: minimum clinically important difference. *** P<0.001 vs. placebo (statistical analysis assessed via two-way ANOVA).

3.3. Asthma events

Doxofylline 400 mg and theophylline 250 mg both significantly (p<0.05) reduced the rate of asthma events compared to baseline after 12 weeks of treatment (events/day: -0.55±0.18 and -0.57±0.17, respectively). Doxofylline 400 mg and theophylline 250 mg also significantly (P<0.001) improved the change from baseline (measured during run-in phase) in asthma events rate vs. placebo during the study period (Figure 3). No significant (P<0.05) difference were detected between doxofylline 400 mg and theophylline 250 mg with respect to asthma events rate from week 2 onwards (absolute difference in events/day: 0.05±0.15).

Figure 3. Impact of doxofylline 400 mg, theophylline 250 mg and placebo on the change from baseline in asthma events rate (events/day), as measured during clinic visits. *** P<0.001 vs. placebo (statistical analysis assessed via two-way ANOVA).
3.4. Rescue medication

Doxofylline 400 mg and theophylline 250 mg both significantly (P<0.05) reduced the use of salbutamol compared to baseline (measured during run-in phase) after 12 weeks of treatment (puffs/day: -1.10±0.34 and -1.14±0.33, respectively). Doxofylline 400 mg and theophylline 250 mg also significantly (p<0.01 and p<0.001, respectively) reduced the use of rescue medication vs. placebo during the study period (Figure 4). No significant (P<0.05) difference were detected between doxofylline 400 mg and theophylline 250 mg with respect to the use of salbutamol from week 2 onwards (absolute difference in puffs/day: 0.09±0.30).

![Figure 4](image)

**Figure 4.** Impact of doxofylline 400 mg, theophylline 250 mg and placebo on the change from baseline in salbutamol use rate (puffs/day), as measured during clinic visits. *** P<0.001 and ** P<0.01 vs. placebo (statistical analysis assessed via two-way ANOVA).

3.5. Safety profile

The safety profile of doxofylline 400 mg (the overall risk of AEs) was not significantly higher that what was encountered with placebo (RR 1.16 CI95%
0.95 – 1.42), conversely in patients treated with theophylline 250 mg the overall risk of AEs was significantly (p<0.05) greater than in those that received placebo (RR 1.27 CI 95% 1.05 – 1.55). Specifically, theophylline 250 mg significantly increased the risk of nausea (RR 2.29 CI 95% 1.41 – 3.71, p<0.001), nervousness (RR 3.50 CI 95% 1.55 – 7.92, p<0.001), insomnia (RR 6.74 CI 95% 2.04 – 22.33, p<0.001), and overdose (serum theophylline level above 20 µg/mL, RR 8.57 CI 95% 1.08 – 67.71, p<0.001) compared to placebo. Although doxofylline 400 mg did not modulate the overall risk of AE, in patients treated with doxofylline 400 mg the risk of insomnia was significantly greater than in those treated with placebo (RR 4.34 CI 95% 1.23 – 15.11, P<0.01). Table 2 shows the detailed frequency of AEs in the treatments groups. The withdrawal due to AEs was significantly (p<0.01) greater in patients treated with theophylline 250 mg than in those that received doxofylline 400 mg (RR 2.30 CI95% 1.33 – 3.98).

Table 2. Summary of frequency of AEs (sorted by descending order) resulting by the pooled analysis of DOROTHEO 1 and DOROTHEO 2 studies.

|                      | Doxofylline 400 mg | Theophylline 250 mg | Placebo  |
|----------------------|-------------------|--------------------|---------|
| Total number (%) of subjects | 163               | 155                | 165     |
| Number (%) of subjects reporting at least one AE | 95 (57.67)         | 98 (63.23)         | 82 (49.70) |
| Total number of AEs |                   |                    |         |
| Headache             | 46 (28.22)        | 47 (30.32)         | 45 (27.27) |
| Nausea               | 25 (15.34)        | 43 (27.74)         | 20 (12.12) |
| Nervousness          | 8 (4.91)          | 23 (14.84)         | 7 (4.24)  |
| Insomnia             | 13 (7.98)         | 19 (12.26)         | 3 (1.82)  |
| Dyspepsia            | 12 (7.36)         | 14 (9.03)          | 7 (4.24)  |
| Diarrhoea            | 7 (4.29)          | 7 (4.52)           | 12 (7.27) |
| Vomiting             | 8 (4.91)          | 9 (5.81)           | 3 (1.82)  |
| Rhinitis             | 8 (4.91)          | 6 (3.87)           | 0 (0.00)  |
| Overdose             | 0 (0.00)          | 8 (5.16)           | 0 (0.00)  |
| Dizziness            | 8 (4.91)          | 7 (4.52)           | 7 (4.24)  |
| Asthma               | 7 (4.29)          | 7 (4.52)           | 8 (4.85)  |
| Abdominal pain       | 6 (3.68)          | 4 (2.58)           | 8 (4.85)  |
| Pharyngitis          | 4 (1.84)          | 5 (3.23)           | 6 (3.64)  |
| Chest pain           | 5 (3.07)          | 0 (0.00)           | 1 (0.61)  |
| Somnolence           | 1 (0.61)          | 1 (0.65)           | 5 (3.03)  |
| Asthenia             | 0 (0.00)          | 4 (2.58)           | 0 (0.00)  |
| Palpitations         | 4 (2.45)          | 4 (2.58)           | 3 (1.82)  |
| Cough increased      | 1 (0.61)          | 4 (2.58)           | 1 (0.61)  |

AE: adverse events.

Three serious AEs (SAEs) were recorded in the doxofylline group (1 asthma exacerbation, 1 systemic reaction to immunotherapy, 1 cold leading to asthma...
exacerbation), 1 SAE was detected in the theophylline group (severe asthma exacerbation), and 1 SAE was reported in the placebo group (degenerative disk disease). Among these SAEs, only the severe asthma exacerbation in the theophylline group was classified by the investigator to be possibly related to study medication, the other SAEs were classified to be not drug related.

No subjects died during the studies or within 30 days after finishing the studies.

4. Discussion

This pooled analysis of DOROTHEO 1 and DOROTHEO 2 studies [22, 23] showed that over 12 weeks, treatment with doxofylline 400 mg and theophylline 250 mg both significantly increased 2-h postdose FEV₁ compared to baseline in asthmatic patients, and that such improvements exceeded the MCID from week 2 onwards. The overall improvement in the change from baseline in 2-h postdose FEV₁ was similar between doxofylline 400 mg and theophylline 250 mg, and significantly greater than that elicited by placebo. Similarly, both doxofylline 400 mg and theophylline 250 mg were effective in reducing the rate of asthma events and use of salbutamol to relieve asthma symptoms compared to baseline. In this regard, both medications were significantly more effective than placebo during the study period, and no difference in efficacy was detected between the active treatments. Interestingly, the trend of improvement elicited by doxofylline 400 mg and theophylline 250 mg with respect to the rate of asthma events was similar to that of salbutamol use. This evidence suggests that metrics of salbutamol used as rescue medication may predict the rate of asthma events, and further supports previous findings indicating that higher daily salbutamol use was associated with future severe exacerbations, poor asthma control, and increased risk of future extreme salbutamol overuse [27].

Indeed, we cannot omit that also placebo had a certain effect on the outcome assessed in this pooled analysis, although placebo was always significantly less effective than both doxofylline 400 mg and theophylline 250 mg during
the study period and did not reach the MCID for the change from baseline in \( \text{FEV}_1 \). Abnormally high responses to placebo are not infrequently reported with no apparent explanation in randomized controlled trials [28]. However, we can explain such an unexpected level of placebo effect by considering that better adherence to drug regimens in the context of a clinical trial may have contributed to this observation, as recently reported in severe asthmatic patients with respect to the percentage reduction in oral glucocorticoid dose and change from baseline in \( \text{FEV}_1 \) [29, 30].

Doxofylline 400 mg showed a favourable safety profile that was significantly superior to that of theophylline 250 mg. In fact, AEs leading to drop-outs occurred more frequently with theophylline 250 mg than doxofylline 400 mg. Furthermore, while the only significant AE in patients receiving doxofylline 400 mg was insomnia, in subject treated with theophylline a significant higher risk of nausea, nervousness, insomnia, and overdose was detected compared to placebo.

The findings of this pooled analysis confirm the recent evidence rose from meta-analyses aimed to assess the functional and clinical impact of xanthines in COPD [1, 2]. Specifically, doxofylline produced a large to very large improvement in lung function and reduced dyspnoea similarly to theophylline, and the use of doxofylline was associated with a significantly better safety profile than theophylline [1, 2]. Overall, in COPD patients doxofylline showed a more favourable efficacy/safety profile than theophylline [1]. Results of this pooled analysis are also in line with a previous study reporting the efficacy and safety profile of doxofylline compared to theophylline in asthmatic patients [19].

Although this pooled analysis and previous studies demonstrated that the treatment with xanthines might significantly improve lung function and symptoms in asthmatic patients and subjects with COPD, their therapeutic use has declined substantially in recent years [1, 2, 19]. The development of ICSs has significantly altered the therapeutic approach to asthma in most part of the world [31]. Nonetheless, nowadays, new evidence appears to support a reappraisal in the use of these drugs [32].
Theophylline is usually less effective than ICS, but, when used in combination with low-to-medium doses of an ICS, the same effects as those obtained with an increased inhaled corticosteroid dose can be achieved in asthmatic patients [33]. Therefore, theophylline can be recommended when asthma control cannot be achieved by using ICSs. With the introduction of doxofylline a new window of opportunity has opened up as a result of a similar efficacy and better tolerability than theophylline to treat patients suffering from chronic obstructive respiratory disorders, such as asthma and COPD [1, 2, 7, 34-40]. Doxofylline demonstrated significant anti-inflammatory activity in the lung which can result in significant steroid sparing activity [41]. Rajanandh and colleagues [42] have recently demonstrated that doxofylline was as effective as montelukast and tiotropium, all in association with low-dose inhaled steroids, in relieving airways obstruction asthmatic patients. The use of xanthines, and particularly of doxofylline, could be particularly valuable in elderly patients with asthma or smoker subjects, where other drugs, especially ICSs, are less likely to work due to the inhibition of histone deacetylase 2 (HDAC2) activity [43]. Finally, Mennini and colleagues [44] have provided evidence of the cost-effectiveness of doxofylline. Although, theophylline has an average base price lower than doxofylline, physicians can be recommended to prescribe it instead of theophylline not only for its favourable efficacy/safety profile, but also because it has been demonstrated that doxofylline can reduce the costs associated with the management of respiratory disorders [44].

Some limitations should be acknowledged with respect to this pooled analysis. A remarkably high dropout rate of approximately 40% in the theophylline group can be considered a major drawback [19, 45], although this highlights the problems related with the tolerability of theophylline. Nevertheless, the average adherence of clinical trials reported in the literature is between 43% to 78% [46], and the overall adherence of this pooled analysis was about 70%. As far as the question whether the better tolerability profile of doxofylline was real or “wishful thinking”, it is important to note that the occurrence of AEs typical of xanthine medications, such as dyspepsia,
nausea, vomiting, dizziness, and insomnia [1, 2], were more frequent in patients who were given theophylline than in those who received doxofylline.

5. Conclusion

In line with the assumption that xanthines still play an important role in treatment of asthma, from the results of this pooled analysis we can conclude that doxofylline is a xanthine bronchodilator with valuable characteristics by functional and clinical viewpoint. Since doxofylline was associated with improved bronchodilatory response, reduced rate of asthma events, reduced use of salbutamol as rescue medication and fewer AEs, it seems to offer a promising alternative to theophylline in the management of patients with asthma.
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7. References

[1] Cazzola M, Calzetta L, Barnes PJ, Criner GJ, Martinez FJ, Papi A, et al. Efficacy and safety profile of xanthines in COPD: a network meta-analysis. Eur Respir Rev. 2018;27.

[2] Cazzola M, Calzetta L, Rogliani P, Page C, Matera MG. Impact of doxofylline in COPD: A pair-wise meta-analysis. Pulm Pharmacol Ther. 2018.

[3] Barnes PJ. Theophylline. Am J Respir Crit Care Med. 2013;188:901-6.

[4] Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. Pharmacol Rev. 2012;64:450-504.

[5] Shukla D, Chakraborty S, Singh S, Mishra B. Doxofylline: a promising methylxanthine derivative for the treatment of asthma and chronic obstructive pulmonary disease. Expert Opin Pharmacother. 2009;10:2343-56.

[6] Spina D, Page CP. Xanthines and Phosphodiesterase Inhibitors. Handb Exp Pharmacol. 2017;237:63-91.

[7] Page CP. Doxofylline: a "novofylline". Pulm Pharmacol Ther. 2010;23:231-4.

[8] Franzzone JS, Cirillo R, Barone D. Doxofylline and theophylline are xanthines with partly different mechanisms of action in animals. Drugs Exp Clin Res. 1988;14:479-89.

[9] Cirillo R, Barone D, Franzzone JS. Doxofylline, an antiasthmatic drug lacking affinity for adenosine receptors. Arch Int Pharmacodyn Ther. 1988;295:221-37.

[10] Dolcetti A, Osella D, De Filippis G, Carnuccio C, Grossi E. Comparison of intravenously administered doxofylline and placebo for the treatment of severe acute airways obstruction. J Int Med Res. 1988;16:264-9.

[11] Poggi R, Brandolese R, Bernasconi M, Manzin E, Rossi A. Doxofylline and respiratory mechanics. Short-term effects in mechanically ventilated patients with airflow obstruction and respiratory failure. Chest. 1989;96:772-8.

[12] Zhou B, Cai SX, Zou F, Cai CQ, Zhao HJ. [Effect of doxofylline on calcium-activated potassium channels in human peripheral blood eosinophils in asthma]. Zhonghua Jie He He Hu Xi Za Zhi. 2005;28:817-9.

[13] Franzzone JS, Cirillo R, Biffignandi P. Doxofylline exerts a prophylactic effect against bronchoconstriction and pleurisy induced by PAF. Eur J Pharmacol. 1989;165:269-77.

[14] Sugeta A, Imai T, Idaira K, Horikoshi S, Okamoto M, Adachi M. [Effects of theophylline and doxofylline on airway responsiveness in beagles]. Arerugi. 1997;46:7-15.

[15] Santra CK. Treatment of moderate chronic obstructive pulmonary disease (stable) with doxofylline compared with slow release theophylline--a multicentre trial. J Indian Med Assoc. 2008;106:791-2, 4.

[16] Melillo G, Balzano G, Jodice F, De Felice A, Campisi V, Capone M, et al. Treatment of reversible chronic obstruction with doxofylline compared with slow-release theophylline: a double-blind, randomized, multicentre trial. Int J Clin Pharmacol Res. 1989;9:396-405.

[17] Bossi R, Berni F. Double blind multicenter trial on efficacy and tolerability of doxofylline vs aminophylline in patients with chronic airway obstruction and reversible bronchospasm. Italian Journal of Chest Diseases. 1989;43:355-60.

[18] Margay SM, Farhat S, Kaur S, Teli HA. To study the efficacy and safety of doxofylline and theophylline in bronchial asthma. Journal of clinical and diagnostic research : JCDR. 2015;9:FC05-8.

[19] Goldstein MF, Chervinsky P. Efficacy and safety of doxofylline compared to theophylline in chronic reversible asthma -- a double-blind randomized placebo-controlled multicentre clinical trial. Med Sci Monit. 2002;8:CR297-304.

[20] Matera MG, Page C, Cazzola M. Doxofylline is not just another theophylline! Int J Chron Obstruct Pulmon Dis. 2017;12:3487-93.
[21] Lal D, Manocha S, Ray A, Vijayan VK, Kumar R. Comparative study of the efficacy and safety of theophylline and doxofylline in patients with bronchial asthma and chronic obstructive pulmonary disease. J Basic Clin Physiol Pharmacol. 2015;26:443-51.

[22] Impact of DOxofylline compaRed IO THEOphylline in asthma: the DOROTHEO 1 study. Available at https://doi.org/10.1186/ISRCTN65297911. ISRCTN registry. 2018.

[23] Impact of DOxofylline compaRed IO THEOphylline in asthma: the DOROTHEO 2 study. Available at https://doi.org/10.1186/ISRCTN22374987. ISRCTN registry. 2018.

[24] Sullivan KM, Dean A, Soe MM. OpenEpi: a web-based epidemiologic and statistical calculator for public health. Public Health Rep. 2009;124:471.

[25] Tepper RS, Wise RS, Covar R, Irvin CG, Kercsmar CM, Kraft M, et al. Asthma outcomes: pulmonary physiology. J Allergy Clin Immunol. 2012;129:S65-87.

[26] Sullivan KM, Dean A, Soe MM. OpenEpi: a web-based epidemiologic and statistical calculator for public health. Public Health Rep. 2009;124:471.

[27] Zubieta JK, Stohler CS. Neurobiological mechanisms of placebo responses. Ann N Y Acad Sci. 2009;1156:198-210.

[28] Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. N Engl J Med. 2018.

[29] Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. N Engl J Med. 2018.

[30] Perrotta F, Mazzeo F, Cerqua FS. Which treatment for obstructive airway disease: The inhaled bronchodilators. Pulm Pharmacol Ther. 2017;43:55-7.

[31] Spina D, Page CP. Xanthines and phosphodiesterase inhibitors. Pharmacology and Therapeutics of Asthma and COPD: Springer; 2016. p. 63-91.

[32] Evans DJ, Taylor DA, Zetterstrom O, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. N Engl J Med. 1997;337:1412-8.

[33] Lazzaroni M, Grossi E, Bianchi Porro G. The effect of intravenous doxofylline or aminophylline on gastric secretion in duodenal ulcer patients. Aliment Pharmacol Ther. 1990;4:643-9.

[34] Sacco C, Braghiroli A, Grossi E, Donner CF. The effects of doxofylline versus theophylline on sleep architecture in COPD patients. Monaldi Arch Chest Dis. 1995;50:98-103.

[35] De Sarro A, Grasso S, Zappalà M, Nava F, De Sarro G. Convulsant effects of some xanthine derivatives in genetically epilepsy-prone rats. Naunyn-Schmiedeberg's archives of pharmacology. 1997;356:48-55.

[36] Dini FL. Chronotropic and arrhythmogenic effects of two methylxanthine bronchodilators, doxofylline and theophylline, evaluated by holter monitoring. Comparison with experimental in vitro and in vivo results. Curr Ther Res. 1991;49:978-85.

[37] Dini FL, Cogo R. Doxofylline: a new generation xanthine bronchodilator devoid of major cardiovascular adverse effects. Curr Med Res Opin. 2000;16:258-68.

[38] van Mastbergen J, Jolas T, Allegra L, Page CP. The mechanism of action of doxofylline is unrelated to HDAC inhibition, PDE inhibition or adenosine receptor antagonism. Pulm Pharmacol Ther. 2012;25:55-61.

[39] Riffo-Vasquez Y, Man F, Page CP. Doxofylline, a novofylline inhibits lung inflammation induced by lipopolysaccharide in the mouse. Pulm Pharmacol Ther. 2014;27:170-8.
[41] Riffo-Vasquez Y, Venkatasamy R, Page CP. Steroid sparing effects of doxofylline. Pulm Pharmacol Ther. 2018;48:1-4.

[42] Rajanandh MG, Nageswari AD, Ilango K. Assessment of montelukast, doxofylline, and tiotropium with budesonide for the treatment of asthma: which is the best among the second-line treatment? A randomized trial. Clin Ther. 2015;37:418-26.

[43] Matera MG, Calzetta L, Gritti G, Gallo L, Perfetto B, Donnarumma G, et al. Role of statins and mevalonate pathway on impaired HDAC2 activity induced by oxidative stress in human airway epithelial cells. Eur J Pharmacol. 2018;832:114-9.

[44] Mennini FS, Sciattella P, Marcellusi A, Marcobelli A, Russo A, Caputi AP. Treatment plan comparison in acute and chronic respiratory tract diseases: an observational study of doxofylline vs. theophylline. Expert Rev Pharmacoecon Outcomes Res. 2017;17:503-10.

[45] Bense L. Conclusion without support-remarks on ‘Efficacy and safely of doxyphyllin compared to Theophylline in chronic reversible asthma-a double-blind randomized placebo-controlled multicentre trial’ by Goldstein MF, Chervinsky P (published in MedSciMonit, 2002; 8 (4): CR297-304. Med Sci Monit. 2002;8:LE27-LE8.

[46] Breckenridge A, Aronson JK, Blaschke TF, Hartman D, Peck CC, Vrijens B. Poor medication adherence in clinical trials: consequences and solutions. Nat Rev Drug Discov. 2017;16:149-50.