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Impact of DOxofylline compaRed tO THEOphylline in asthma: the DOROTHEO 1 study

Submission date
17/05/2018

Recruitment status
No longer recruiting

Registration date
01/06/2018

Overall study status
Completed

Last Edited
21/06/2018

Condition category
Respiratory

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Doxofylline is a drug belonging to the class methylxanthines, which also includes theophylline. Doxofylline has shown similar efficacy to theophylline in asthmatic patients but with significantly fewer side effects. Unlike other xanthines such as theophylline, doxofylline does not activate certain specific cellular receptors (i.e. adenosine receptors) and does not alter the movement of calcium into cells. These specific characteristics may account for the better safety profile of doxofylline compared to theophylline. Conversely, the anti-asthmatic effects of doxophylline involve other mechanisms, mainly reducing the activity of intracellular enzymes (i. e. phosphodiesterases). Thus, the aim of this study is to investigate the beneficial impact of doxofylline versus theophylline with regard to efficacy and safety in asthmatic patients.

Who can participate?
Adult (over 16 years old) asthmatic patients

What does the study involve?
Participants are randomly allocated to receive 3 months oral treatment three times daily with placebo (dummy drug), doxofylline 200 mg, doxofylline 400 mg or theophylline 250 mg. Lung function tests are carried out at day 1 and at weeks 2, 4, 6, 8, 10 and 12.

What are the possible benefits and risks of participating?
The possible benefits may include increased lung function, reduced asthma attack rate, and reduced use of albuterol, leading to an overall increased asthma control. The potential risks may include the occurrence of side effects, namely gastrointestinal symptoms (nausea, vomiting, gastrointestinal distress, stomach ache), tachycardia or palpitations, insomnia, and nervousness. In any case, the overall treatment benefits would overcome the symptoms related with the side effects.

Where is the study run from?
Family Practice Residency Program, Jacksonville, FL (US); Delaware Valley Lung Center, Cherry Hill, NJ (US); Allergy & Immunology, Inc., Stockton, CA (US); Medical Research Group, Salt Lake

City, UT (US); Allergy Associates, Inc., North Dartmouth, MA (US); International Medical Technical Consultants, Inc., Prairie Village, KS (US); Advanced Allergy & Asthma, Albany, NY (US); Pulmonary Associates, Philadelphia, PA (US); Asthma & Allergy Research Center, Orange, CA (US); Allergic Disease Associates, Philadelphia, PA (US); Pharmaceutical Research & Consulting, Inc., Dallas, TX (US); Doctors' Clinic Research Center, Vero Beach, FL (US); Pharmaco Health Research Center, Austin, TX (US); Allergy Asthma Care, Cranford, NJ (US); El Paso Institute for Medical Research and Development, El Paso, TX (US); Allergy and Asthma Consultants, P.A., Tinton Falls, NJ (US); University of Arizona Health Science Center, Tucson, AZ (US); Allergy Research Foundation, Inc., Los Angeles, CA (US); Creighton University School of Medicine, Omaha, NE (US).

When is the study starting and how long is it expected to run for?
September 1990 to November 1994

Who is funding the study?
Roberts Pharmaceutical Corporation (USA)

Who is the main contact?
Dr Alberto Giraudi
alberto.giraudi@abcfarmaceutici.it

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Protocol serial number
30,722-301D

Study information

Scientific Title
A double-blind Phase III evaluation of doxofylline, theophylline, and placebo in patients with chronic reversible asthma

Acronym
DOROTHEO 1

Study objectives
Doxofylline [2-(7'-theophylline-methyl)-1,3-dioxolane] is a methylxanthine derivative with the presence of a dioxolane group in position 7. As a drug used in the treatment of asthma, doxofylline has shown similar efficacy to theophylline but with significantly fewer side effects in animal and human studies. Unlike other xanthines, doxofylline lacks any significant affinity for adenosine A1 or A2 receptors and does not produce stimulant effects. Decreased affinity for adenosine receptors may account for the better safety profile of doxofylline compared to theophylline. Unlike theophylline, doxofylline does not affect calcium influx and does not antagonize the actions of calcium channel blockers which could explain reduced cardiac adverse reactions associated with the drug. The anti-asthmatic effects of doxophylline are mediated by other mechanisms, primarily through inhibiting the activities of the phosphodiesterase (PDE) enzymes.

Therefore, the hypothesis of this study was that doxofylline may have the same efficacy profile of theophylline, and that doxofylline may have a greater safety profile compared to theophylline in patients with asthma.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Lead centre ethics board: The Asthma Center, Philadelphia, PA, USA, 13/05/1991, ref: 30,722-301D-91

The study protocol was reviewed and approved by Institutional Review Boards (IRBs) at the following study sites:
Family Practice Residency Program, Jacksonville, FL (US); Delaware Valley Lung Center, Cherry Hill, NJ (US); Allergy & Immunology, Inc., Stockton, CA (US); Medical Research Group, Salt Lake City, UT (US); Allergy Associates, Inc., North Dartmouth, MA (US); International Medical Technical Consultants, Inc., Prairie Village, KS (US); Advanced Allergy & Asthma, Albany, NY (US); Pulmonary Associates, Philadelphia, PA (US); Asthma & Allergy Research Center, Orange, CA (US); Allergic Disease Associates, Philadelphia, PA (US); Pharmaceutical Research & Consulting, Inc., Dallas, TX (US); Doctors' Clinic Research Center, Vero Beach, FL (US); Pharmaco Health Research Center, Austin, TX (US); Allergy Asthma Care, Cranford, NJ (US); El Paso Institute for Medical Research and Development, El Paso, TX (US); Allergy and Asthma Consultants, P.A., Tinton Falls, NJ (US); University of Arizona Health Science Center, Tucson, AZ (US); Allergy Research Foundation, Inc., Los Angeles, CA (US); Creighton University School of Medicine, Omaha, NE (US)

Study design
Multicenter double-blind randomized placebo-controlled Phase III clinical trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Asthma

Interventions
Subjects were randomly assigned to one of the four treatment groups in blocks of four patients according to a computer-generated randomization schedule prepared by the sponsor.
Participants receive 3 months oral therapy as follows:
1. Placebo t.i.d.
2. Doxofylline 200 mg t.i.d.
3. Doxofylline 400 mg t.i.d.
4. Theophylline 250 mg t.i.d.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Doxofylline, theophylline

Primary outcome(s)
The primary outcome was the forced expiratory volume in 1 s (FEV1). The derived variable that was considered for comparative assessments among treatments was the percent change in the 2 hours FEV1 value from the baseline value (T0, hour 0). The primary timepoint was the last observation that was reported for each subject during the double-blind treatment period (3 months). FEV1 values were measured by using pulmonary function tests (PFTs) at day 1 (T0) and after at week 2, week 4, week 6, week 8, week 10, week 12.

Key secondary outcome(s))
1. The secondary outcome variables were forced vital capacity (FVC), FEV1/FVC, forced expiratory flow during the middle half of the FVC (FEF25%-75%) and peak expiratory flow rate (PEFR). These outcomes were expressed as the percent change in the 2 hours values from the baseline value (T0, hour 0). The endpoint was the last observation that was reported for each subject during the double-blind treatment period (3 months). These secondary outcomes were measured by using PFTs at day 1 (T0) and after at week 2, week 4, week 6, week 8, week 10, week 12.
2. Secondary efficacy variables derived from the Medication/Symptom Diaries were asthmatic attack rate (total number of attacks divided by the total number of days on study medication), albuterol use rate (total number of puffs divided by total number of days on study medication), average daily peak flow meter (PFM) rate, and global assessment. For the daily PFM rate, the percent change from baseline (T0) was calculated. For the remaining efficacy variables derived from the Medication/Symptom Diaries, the absolute change from baseline (T0) was determined. “Baseline” for these variables was defined as the value obtained from the diaries during the placebo run-in phase, after that these secondary outcomes were measured at week 2, week 4, week 6, week 8, week 10, week 12.
3. Safety was assessed by physical examinations, ECGs, and the recording of vital signs, laboratory test results, and adverse events. All clinical adverse events (AE) entered on the Case Report Forms (CRFs) were to be classified as to possible relation to study medication (not related, possibly related, definitely related, or unknown) and severity (mild, moderate, or severe). Also recorded for each AE were the start and stop dates, the action taken (none, study medication discontinued, or treatment prescribed), and the outcome (recovered, recovered with sequelae, under treatment, deceased, unknown, or ongoing). If a subject experienced an AE leading to withdrawal from the study, the investigator was to make an effort to have the subject

return to the study center for examination and for obtaining a serum sample for drug level determination. The time and date of the last dose taken were to be entered into the CRF.

Completion date
02/04/1997

Eligibility

Key inclusion criteria
1. Males and nonpregnant females. Women of childbearing potential had to use acceptable methods of birth control and have a negative prestudy serum β-hCG pregnancy test. Acceptable methods of birth control were limited to vaginal or intrauterine contraceptive devices or agents and natural (postmenopausal) or surgical sterility. Abstention, oral contraceptives, and use of contraceptive by the woman's partner were not acceptable methods of birth control
2. Age: adults, 16 years of age or older
3. Health status: nonsmokers for at least 6 months before entering the study, in good physical condition with a more than 1-year history of chronic, extrinsic reversible hyperreactive airway disease (asthma)
4. Willing to undergo the procedures required in the protocol
5. Willing to undergo a chest x-ray if required by the Principal Investigator
6. On screening, subjects must have had a baseline FEV1 value within 50% to 80% of the predicted FEV1 value for their age and height, when immediate-release theophylline or sustained-release theophylline had been withheld for at least 24 hours. Subjects were further required to have abstained from use of any sympathomimetic, including beta-agonist inhalers, for at least 8 hours before the screening pulmonary function tests (PFTs)
7. On screening, subjects had to show at least a 15% increase in FEV1 30 minutes after administration of a standard dose (2 puffs, 180 µg) of albuterol
8. Subjects must have demonstrated, by verbal history, a period of at least 1 month of acceptable clinical control of their asthma in the preceding 3 years using oral theophylline, alone or in combination with a beta-agonist inhaler
9. Subjects had to weight at least 48 kg (105 lb)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Clinically significant deviation from normal in physical examination, laboratory parameters, ECG, or chest x-ray, as evaluated by the Principal Investigator, that would have precluded the

subject’s participation in the study
2. Clinically significant coexisting disease, including:
2.1. Clinically significant cardiovascular disease, including a history of congestive heart failure
2.2. Angina pectoris within 1 year
2.3. History of myocardial infarction within 1 year
2.4. Convulsive disorder
2.5. Clinically significant gastrointestinal disease, including active peptic ulcers within the preceding 5 years
2.6. Renal disease
2.7. Hepatic disease
2.8. Hematologic disease
2.9. Insulin-dependent diabetes mellitus
2.10. Nonreversible chronic pulmonary disease
2.11. Known infection with human immunodeficiency virus
2.12. Chronic obstructive pulmonary disease
3. Presence of any acute illness
4. Sensitivity to theophylline or theophylline-like agents
5. A resting heart rate of less than 50 bpm or greater than 100 bpm and/or an arterial blood pressure of less than 100/60 mmHg or greater than 140/90 mmHg when sitting
6. History of alcohol, narcotic, barbiturate, marijuana, or polydrug abuse
7. Participation in other investigational drug studies within 30 days before the start of this study
8. Subjects who were unlikely to be compliant with the protocol requirements
9. Oral contraceptive use was not allowed because of the propensity for these drugs to decrease theophylline clearance. If a woman became pregnant during the study, she was to be withdrawn from the study
10. Nursing mothers
11. Subjects using aerosol steroids were required to discontinue their use at least 1 month before the study and to refrain from using them throughout the entire study. Subjects using oral steroids to control bronchoconstriction were excluded from participation. Subjects using cromolyn sodium or oral steroids were required to discontinue their use at least 1 month before the study and to refrain from using them throughout the entire study, with the exception of acute steroid burst treatment
12. Due to their effects on theophylline clearance, none of the following could be taken during the study: allopurinol, ciprofloxacin, erythromycin, troleandomycin, lithium carbonate, phenytoin, rifampin, or cimetidine

Date of first enrolment
13/08/1991

Date of final enrolment
28/11/1994

Locations

Countries of recruitment
United States of America

Study participating centre

Family Practice Residency Program
Jacksonville
United States of America
32206

Study participating centre
Delaware Valley Lung Center
Cherry Hill
United States of America
08003

Study participating centre
Allergy & Immunology, Inc.
Stockton
United States of America
95207

Study participating centre
Medical Research Group
Salt Lake City
United States of America
84111

Study participating centre
Allergy Associates, Inc.
North Dartmouth
United States of America
02747

Study participating centre
International Medical Technical Consultants, Inc.
Prairie Village
United States of America
64108

Study participating centre

Advanced Allergy & Asthma
Albany
United States of America
12203

Study participating centre
Pulmonary Associates
Philadelphia
United States of America
19140

Study participating centre
Asthma & Allergy Research Center
Orange
United States of America
92868

Study participating centre
Allergic Disease Associates
Philadelphia
United States of America
19107

Study participating centre
Pharmaceutical Research & Consulting, Inc.
Dallas
United States of America
75231

Study participating centre
Doctors' Clinic Research Center
Vero Beach
United States of America
32960

Study participating centre

Pharmaco Health Research Center
Austin
United States of America
78705

Study participating centre
Allergy Asthma Care
Cranford
United States of America
07066

Study participating centre
El Paso Institute for Medical Research and Development
El Paso
United States of America
79905

Study participating centre
Allergy and Asthma Consultants, P.A.
Tinton Falls
United States of America
07701

Study participating centre
University of Arizona Health Science Center
Tucson
United States of America
85721

Study participating centre
Allergy Research Foundation, Inc.
Los Angeles
United States of America
91356

Study participating centre

Creighton University School of Medicine
Omaha
United States of America
68178

Sponsor information

Organisation
Roberts Pharmaceutical Corporation

Organisation
ABC farmaceutici

Organisation
Takeda (United States)

ROR
https://ror.org/03bygaq51

Funder(s)

Funder type
Industry

Funder Name
Roberts Pharmaceutical Corporation

Funder Name
ABC farmaceutici

Results and Publications

Individual participant data (IPD) sharing plan
Dr Alberto Giraudi (alberto.giraudi@abcfarmaceutici.it) can be contacted for accessing to the datasets. Available data include patient-by-patient variable recorded at each time-point and will be available for request in one year from the publication of the paper. Informed consent was

obtained by all the participants of the study. Data will be shared merely for scientific purposes (i. e. post-hoc analyses, pooled analyses) with researchers employed at institutional research departments who will make a formal request to the scientific board of ABC Farmaceutici. If the scientific board determine the proposed analysis is consistent with the local ethics and legal rules, and could provide further evidence than those published, the data will be released in agreement with patients' anonymisation. The data will be available for one year from the date of publication in a high-impact peer reviewed journal.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		01/06/2018	21/06/2018	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes