Eprost ID: 20170552
NCT Number: NCT03270332
Version Date: 04 August 2021

Effect of inhaled albuterol on pulmonary hemodynamics in patients with group 1 pulmonary arterial hypertension on oral pulmonary vasodilator therapy: A proof of concept study

Adam Wanner1, Barry Hurwitz[2], David De la Zerda1, Eliana S Mendes[1]

[1]Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, University of Miami Miller School of Medicine
[2] Department of Psychology & Department of Biomedical Engineering, University of Miami

Abstract

Inhaled J32-adrenergic agonists have been shown to reduce pulmonary vascular resistance (PVR) in hypoxic COPD patients, and right ventricular systolic pressure in normoxic COPD patients with mild pulmonary hypertension (PH). Furthermore, we have recently found that inhaled albuterol lowers PVR as assessed by echocardiography in healthy smokers and non-smokers (Chest 2017; 151: 650-657). While the pulmonary vascular effects of J32-adrenergic agonists could be indirectly related to the drug's bronchodilator action in patients with COPD, the demonstrated J32-adrenergic agonist induced pulmonary vasodilation in healthy subjects strongly suggests a direct pulmonary vasodilatory effect. This raises the possibility that inhaled J32-adrenergic agonists could cause pulmonary vasodilation in patients with pulmonary hypertension not associated with heart disease, chronic lung disease or thromboembolic disease (WHO group 1 PAH). In the present proof of concept proposal, we will use echocardiography to assess the acute pulmonary hemodynamic effect of albuterol in 6 patients with group 1 PAH documented by right heart catheterization (mean pulmonary arterial pressure >25mmHg, PVR > 3 wood/u and pulmonary wedge pressure <15). The patients will be on regular oral pulmonary vasodilator therapy. Mean pulmonary arterial pressure (MPAP) and cardiac output will be measured before and serially for 2 hours after the administration of either 270µg albuterol or placebo by inhalation using a spacer. PVR will be calculated by using an

estimate of left atrial pressure. This pilot study, if showing that albuterol lowers MPAP and PVR significantly, could form the basis for a phase 2 trial in a larger cohort of patients with group 1 PAH in whom a long acting J32-adrenergic agonist is administered as add-on to commonly used oral pulmonary vasodilators.

Background

While the treatment strategies for PAH are undergoing a paradigm shift away from vasoactive drugs towards tackling the structural remodeling of the pulmonary vasculature, vasodilators still maintain a central position in the currently available treatment modalities. Often, drugs that target different pathways leading to pulmonary vasodilation are administered concomitantly for better effect, especially in patients with group 1 PAH. These drugs include orally administered calcium channel blockers, endothelin receptor blockers and phosphodiesterase-5 inhibitors. J32-adrenergic agonists are potent vasodilators and could be administered by inhalation as add-ons to currently used oral vasodilators in patients with group 1 PAH. Thus far, this possibility has not been explored in this population.

We have previously reported that the short acting J32-adrenergic agonist albuterol, administered by inhalation, markedly and significantly reduced PVR in lung-and heart healthy current smokers and never smokers (1). Other studies involving inhaled J32- adrenergic agonists were carried out in patients with COPD without or with PAH (group 3). Early studies have shown that short-acting J32-adrenergic agonists can reduce PVR in hypoxic COPD patients with PAH (2,3). More recently, Cazzola et al (4) assessed two long-acting J32-adrenergic agents (formoterol and salmeterol) in COPD patients, with or without mild pulmonary hypertension. Following administration of these agents, they observed a reduction in echocardiographic systolic pulmonary arterial pressure that lasted less than 180 min, with a trough minimizing between 15 min and 60 min. It is difficult to separate direct from indirect vasodilation in these studies, i.e. did the J32-adrenergic agonists have a direct effect on the pulmonary circulation or an indirect effect by improving airway function. This caveat also applies to another investigation of albuterol's action in patients with PAH in whom the drug caused both bronchodilation and pulmonary vasodilation at the time of right heart catheterization to assess responses to vasodilators, with the possibility that a change in ventilation/perfusion relationship reversed hypoxic vasoconstriction thereby lowering pulmonary arterial pressure (5).

The purpose of the present pilot study is to test the hypothesis that in patients with group 1 PAH who are on regular oral pulmonary vasodilator

therapy, inhaled albuterol causes transient pulmonary vasodilation. If the results support this premise, they could serve as the basis for a phase 2 trial investigating the potential for using inhaled long-acting 2-adrenergic agonists as add-on therapy in group 1 PAH.

'Research Plan

Test subjects

Ten patients (males and females) over the age of 18 years with group 1PAH will be enrolled on the study. Participants will be recruited from the University of Miami Pulmonary Hypertension Clinic under the direction of Dr. David De la Zerda, a co-investigator.

Inclusion criteria

- A MPAP >25mmHg, PVR>3 wood/units and pulmonary arterial wedge pressure 15mmHg, as documented by right heart catheterization within the last 3 years
- Regular use of oral pulmonary vasodilators

Exclusion criteria

- Presence of chronic respiratory disease (as documented by prior lung imaging and pulmonary function tests), cardiovascular disease (as documented by prior echocardiography and/or left heart catheterization), thromboembolic PAH (as documented by pulmonary angiography)
- women of childbearing potential who do not use accepted birth-control measures
- pregnant and breast-feeding women (vide infra)
- respiratory infection within 4 weeks of testing
- A systemic systolic arterial BP> 150 and/or diastolic arterial BP>100 on the experiment day
- A resting 02 saturation of< 90%
- Current smoking
- BMI >35 kg/m^2 and/or a diagnosis of obstructive sleep apnea
- Use of inhaled or intravenous pulmonary vasodilators

Targeted outcomes

Change in MPAP, PVR after inhalation of 270µg albuterol administered with a spacer. These parameters, measured/calculated by echocardiography, will be obtained before and at 15, 30, 60 and 120 after albuterol or placebo inhalation. At each measurement point, systemic blood pressure, 02 saturation by pulse oximetry and spirometry will also be measured (the latter to rule out drug induced changes in airway function that could indirectly influence pulmonary hemodynamics). We previously have observed that the albuterol response wanes by 60 min in healthy subjects (1). Each participant will serve as his/her own control and the two treatments will be administered on different experiment days in random order. Participants and investigators will be blinded (HFA albuterol and matching placebo are available to the investigators).

Measurements

Echocardiography and calculation of PVR:

Studies will be performed using the SONOS 5500 ultrasound system (Philips Medical Systems) as previously used in our laboratory (1). Measurements will start following 15 min of supine rest. The imaging will proceed according to the following sequence at each time point (baseline and 15, 30, 60, and 120min post-drug administration). Images will be acquired for 1-2 breaths or at least 10 cardiac cycles in order to obtain 3 cycles for quantification. All measurements are made offline. Blood pressure and heart rate will be measured on the final image of each time point measurement using an automated monitor (Dinamap, model 1846XT). Traditionally, the maximum velocity of the tricuspid regurgitation (TRvmax; cm/sec) has been used to calculate pulmonary vascular resistance (PVR). However, this method is not feasible when TR is absent or trivial. Therefore, we will also obtain the pulmonary artery acceleration time (PAAT), which has been shown to correlate highly with invasively measurement of mean pulmonary artery pressure (6). The PAAT will be used as an alternative to the TR method because it does not rely on the presence of an anatomic defect or valvular regurgitation and is highly correlated (r = -.96) with TRvmax (7). TRvmax will be defined as the maximal

velocity of the TR jet measured using continuous-wave Doppler in the 4-chamber view. Estimated peak systolic pulmonary artery pressure (PSPAP) will be calculated using the modified Bernoulli equation: 4 x TRvmax2 + 10mmHg (to account for right atrial pressure) (8). The use of 10mmHg as an estimate of right atrial pressure has been shown to yield similar correlates with catheter-based estimates of right ventricular systolic pressure (RVSP) (9). The PAATwill be measured using the pulse-wave Doppler profile in the parasternal short axis view. PAAT (msec) will be defined as the interval between the onset of systolic pulmonary arterial flow and peak flow velocity. The MPAPPAAT (mm Hg) will be computed by: 79 - (PAAT x 0.45) (9). The right ventricular ejection time (RVET) will also be obtained and defined as the interval between the onset of RV ejection to the point of systolic pulmonary arterial flow cessation. Using pulse-wave Doppler in the 5-chamber view, measures of cardiac function will include stroke volume (SV), wherein SV = 3.14 x (LVOT diameter/2)^2 x VTI. The inter-beat interval is used to derive heart rate (HR) and cardiac output (CO) is the product of SV and HR. Left atrial pressure (LAP) is estimated using Doppler echocardiography (1O); thus, LAP (mm Hg) is computed from the ratio of the E and e' waves of Doppler trans-mitral flow and mitral annulus tissue Doppler imaging as follows: LAP = 1.24 x E/e' +2.

Pulmonary vascular resistance (PVR) will be estimated in two ways based on the estimation of pulmonary artery pressure and LAP: a) as derived from the TR method, PSPAP will be used to estimate mean pulmonary artery pressure (MPAPrR) as follows: MPAPrR = 0.6 x PSPAP +2 (11). Then, the PVRrR is the ratio of (MPAPrR - LAP) and CO; and b) as derived from the PAAT method, the PVRPAAT is the ratio of (MPAPPAAT - LAP) and CO. All values used for analysis will be computed from the average of three cardiac cycles per time point.

Pulmonary function

Spirometry will be done to rule out airflow obstruction (FEV1/FVC <0.7). In the tracing with the highest FVC of three forced vital capacity, FEV1, FVC, FEV1/FVC, IC, MMEF and peak flow will be analyzed. Predicted normal values will be taken from Harkinson NHANES III. The results will be expressed in absolute values and percent of predicted.

Statistical analysis

The study is a repeated-measures design with medication treatment vs. placebo and time post-treatment (pre-inhalation baseline, 15, 30, 60, 120min) as fixed within subject effects. The resulting factorial combinations will permit ANCOVA estimation of the main effects of treatment and time, as well as the 2-way interaction (treatment by time). In addition, ANCOVA analyses will be performed to examine treatment effects on the different outcomes. Significance will be accepted at $p<0.05$.

Procedures

There will be 3 study assessment visits per participant, including the screening visit to confirm study eligibility. Visits 2 and 3 will commence about 9am. The subjects will be asked to keep taking their usual oral pulmonary vasodilator on the experiment days.

Visit 1
On this screening visit, after the subjects have signed an informed consent and HIPAA forms, a medical history will be obtained and then a physical examination will be administered. If they meet screening entry criteria, they will undergo spirometry and the determination of O_2 saturation, blood pressure and heart rate. If the subjects still meet entry criteria, they will be invited to return for visit 2.

Visit 2 and Visit 3
Echocardiographic measurements will be made before and at 15, 30, 60, and 120 min after active drug or placebo inhalation. The choice of drug vs. placebo on each visit will be random, and a double blind procedure will be implemented such that the participants and investigators will not be informed which study agent will be used on these visits. The inhaler used for visit 3 will be the alternate of the one that the subject is randomized to for visit 2.

Safety

There is minimal risk:

Echocardiography
No side effects have been reported.

Pulmonary function tests
There is little risk from spirometry. Some people may have some chest soreness or lightheadedness from the hard blowing. The chest soreness usually is short-lived, but can be treated with non-prescription pain relievers.

Inhaled Albuterol
This drug is approved for clinical use in obstructive lung disease in the US, and will be administered at a clinically recommended dose. Possible serious side effects include chest and muscular pain, tremor, headache, tachycardia, throat irritation, nauseas and vomiting. Although a possible interaction between inhaled albuterol and oral pulmonary vasodilators has not been systematically evaluated to our knowledge, we believe that it is safe to add a f32-adrenergic agonist to oral vasodilators based on clinical experience in patients with co-existing PAH and obstructive lung disease.

Study duration

The total duration of the study will be 6 months from the time of IRS approval. We estimate a total of 30 participant visits (3 visits each for 1Qe enrolled participants plus 4 visits for screen failures) or approximately one visit per week. Screen failures should be rare given the selection criteria and the extensive clinical data available prior to considering a patient for screening.

Recruitment Process

Potential candidates will be identified by the PI and Co-PI in the Pulmonary Hypertension(PH) clinic at the UHealth. If a patient with PH is eligible for the study and agrees to participate in the study, the PI or the Sub-PI will

notify the study coordinator. The Research Team and the PI will present the study to the patient. Eligible patients will be asked to read, comprehend, and sign an informed consent form. This procedure will be performed according to the local regulatory authorities. Potential participants will be given the choice to take a copy of Consent Form to review at home and or discuss with his/her PCP.

No study procedures will be conducted until the informed consent form is previously signed. Participants will have to sign a HIPAA Form as well. A copy of the signed consent and HIPAA Form will be provided to the patient. A review of the subject's medical record will be conducted to confirm that the subject meets inclusion/exclusion criteria as per protocol.

Pregnancy

Taking the study drug may involve unknown risks to a pregnant woman, an embryo, fetus (unborn baby) or nursing infant. Therefore, if female participant is pregnant, planning to become pregnant or are breastfeeding a child, participant cannot participate in this study. In order to reduce the risk of pregnancy, participant must use an effective method of birth control while participating in this study (and for 1 month) after participant complete the study treatment. If participant is already using a method of birth control, the study doctor or study staff will discuss with her whether her current method of birth control is acceptable for use during this study. If, during this study and 30 days after completion of the study, participant becomes pregnant, she should notify the study doctor as soon as possible. The study drug will be stopped and her participation in this study will be ended. Data during pregnancy and pregnancy outcome will be collected. For those females who become pregnant because their male partner is in the study, pregnancy outcome data will not be collected.

Data collection and storage:

Case Report Forms (CRFs) will be provided for each subject. Participants will not be identified by name on any study documents collected by sponsor or its representative but may be identified by an SIN and initials.
The paper records will be kept in a secure location (Pulmonary Research Office) in a locked office with limited access.

All clinical information requested will be recorded in the CRFs .
CRFs must be reviewed and verified for accuracy by the Principal Investigator and signed off before the data is entered on a safety password protected electronic system. A copy of the CRF will remain at the Investigator's site at the completion of the study.

Data Recording

All data will be entered into an electronic database (RedCap). Patients will be provided with a unique study number and only the study team will have access to the database.

Maintenance of data confidentiality

The investigator/delegate will ensure that data confidentiality is maintained. On CRFs or other documents, subjects will be identified only by number, and never by name or initials, hospital numbers, SSN or any other identifier. The investigator/delegate will keep a subject identification code list, at the site, showing the randomization number, the subject's name, date of birth and address or any other locally accepted identifiers. CRFs will be kept at the Pulmonary Research Center located at 1321 NW 14th Street suite 607, Miami Florida 33136 where only study personnel has access to this location.

Database management and quality control

Electronic CRFs will be used for all subjects through RedCap. The investigator will have access to the site CRF data until the database is locked. Thereafter, they will have read-only access. The CRF will be kept current to reflect subject status at any time point during the course of the study.

While entering the data, the investigator/delegate will be instantly alerted to data queries by validated programmed checks. Additional data review will be performed on an ongoing basis to look for unexpected patterns in data and study monitoring by the Principal Investigator. If discrepant data are detected, a query specifying the problem and requesting clarification will be issued and visible to the investigator/delegate via the CRF. All electronic queries visible in the system either require a data correction (when applicable) and/or a response from the investigator/delegate to clarify the queried data directly in the CRF, or simply a data correction in the CRF.

Confidentiality

All information relating to this research protocol will be kept confidential to the extent permitted by law. However, records will be available to the University of Miami IRB, sponsor, appropriate governmental agencies, and by authorized University of Miami employees or other agents authorized by the University. Study staff is HIPAA trained and complied with our Institution requirements.

A file for each subject will be maintained that includes the signed ICF and subject information sheet and the Investigator's copies of all source documentation related to that subject. The Investigator will ensure the reliability and availability of source documents from which the information in the CRF was derived.

Data Security

Access is limited to personnel involved in the study (PI, sub-PI, and the research team).

Settings

Site name and address:
Pulmonary Research Office at the University of Miami Hospital West building, 1321 NW 14th Street Room 607 Miami, Florida 33125.

Informed Consent

Potential participants attending to the PH clinics at the University of Miami will be invited to participate on this registry by the PI or Co-PI. The purpose of the study and procedures will be extensively discussed with the patients. If he/she is willing to participate, the Informed Consent process will take place. Patients will have enough time to decide about participation and if requested taking the ICF to be discussed with family members or PCP. If Hispanic subjects who do not speak English will be enrolled, a translated approved version of the ICF will be provided to the subject. The study staff is bilingual.

Patient reimbursement

Patients will receive $200 for each visit attended with total amount of $600.00. This is to defray costs of time and travel for each visit.

Removal of Subjects from Study

A subject withdrawal is defined as a discontinuation from the study for any reason. Subjects may withdraw or be withdrawn from this study for the following reasons:

- at their own request or at the request of their authorized representative at any time for any reason

- if continuation in the study would be detrimental to the subject's well-being, in the investigator's opinion.

Study Drug

Albuterol will be administered as Ventolin HFA, purchased by the investigator. Ventolin placebo HFA has been provided to the investigators by Glaxo Smith Kline as samples for patient education. The two inhalers will be matched in appearance (label with blinded identifier, covering the entire cartridge, which is the same for active drug and placebo).

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