Title:
A randomized, double blind, crossover trial comparing fexofenadine to placebo for the treatment of proton pump inhibitor (PPI) refractory gastroesophageal reflux symptoms

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Aims:
1. Evaluate the efficacy of fexofenadine in the treatment of proton pump inhibitor (PPI) refractory gastroesophageal reflux disease (GERD).
2. Evaluate side effects and tolerability of fexofenadine in a population of treatment refractory GERD patients.

Background and Rationale:
About 18-28% of North American adults have GERD at least once per week (1). Proton pump inhibitors (PPIs) are common treatments, but as many as 60% of GERD subjects experience heartburn despite use (2-6). While residual acid exposure may play a role in some patients, PPIs are quite effective at reducing acid reflux (7-10). Another possible explanation is that the persistent heartburn represents neuropathic pain. One potential mechanism includes activation of transient receptor potential channel vanilloid subfamily member 1 (TRPV1) (11). These channels are known to be activated by mechanoreceptors (11) and balloon distension can induce heartburn in healthy volunteers (12). In addition, expression of TRPV1 messenger RNA and protein in esophageal mucosa from subjects with both erosive and non-erosive GERD was significantly higher than that in from health subjects (12).

Recently, histamine has been found to sensitize TRPV1 in rectal biopsy specimens from subjects with irritable bowel syndrome via an action mediated by histamine H1-receptors (13). Moreover, in subjects with irritable bowel syndrome, a histamine H1-receptor antagonist reduced visceral hypersensitivity and abdominal pain and increased symptom relief (13).

Fexofenadine is a histamine H1-receptor antagonist that is available over the counter for relief of allergy symptoms. It has a good safety profile and is generally well tolerated (14, 15). We propose to examine the ability of Fexofenadine to relieve heartburn in GERD subjects who experience heartburn or acid regurgitation despite treatment with a PPI.

Significance:
Minimal therapy exists for PPI-refractory GERD, despite being a very common disorder. If positive this trial will potentially add a valuable, safe, and widely available agent for adjunctive therapy.

Research Plan:

Study Design: Randomized, prospective, placebo-controlled, crossover trial
Population: PPI refractory GERD patients with at least 3 episodes of heartburn or reflux per week
Study Sites:

- Stanford Healthcare

Inclusion Criteria:

- Men and women aged >18.
- A minimum 6-month history of heartburn and regurgitation, as their main GERD symptoms.
- Experience at least 3 days with episodes of heartburn or regurgitation while on PPI therapy during the 7 days before randomization (run in period).
- PPI trial of at least one month. If not actively on PPI therapy they must be willing to restart therapy for the trial (a PPI that was used before).
- Need to be on PPI at least 1 week prior to starting the trial
- Female patients who are postmenopausal or using acceptable methods of birth control.

Exclusion Criteria:

- Current or historical evidence of the following GI issues:
    - Esophageal stricture
    - Primary esophageal motility disorder (per Chicago 3.0 classification), ok to have ineffective esophageal motility or fragmented peristalsis, but exclude all others (achalasia, EGJOO, jackhammer, absent peristalsis, distal/diffuse esophageal spasm)
    - Systemic sclerosis
    - Active inflammatory bowel disease
    - Zollinger-Ellison syndrome
    - Active gastric or duodenal ulcer
    - Active infectious or inflammatory conditions of the small or large intestine
    - Malabsorption syndromes
    - History of GI malignancy
    - Prior gastric or intestinal surgery
- Patients with significant co-morbidities including:
    - Decompensated cirrhosis
    - New York Heart Association class III or IV heart failure
    - Renal disease with GFR < 50
    - Pulmonary disease limiting activity or requiring oxygen
    - Malignancy
    - HIV infection
    - Significant psychiatric disease that would prevent participation in the study or accurate reporting of symptoms
    - Transplant
- Unable or unwilling to stop any anti-histamine drugs during the run in period
- Active drug of alcohol abuse
- Pregnancy or breast feeding
- Non-English speaking
- Unable or unwilling to give informed consent.
- Unable or unwilling to comply with study protocol for any reason

Intervention: Fexofenadine capsule 180 PO daily
Comparator: Identical placebo capsule

Trial Length: Total length 6 weeks: 1 week run-in, 2 weeks randomization to placebo vs fexofenadine, 1 week washout, 2 weeks crossover
Primary Outcomes: Mean percentage of GERD free days, Mean number of GERD episodes.
Secondary Outcomes: Mean GERD-HRQL questionnaire score, Mean symptoms severity score (on a scale of 0-4), side effects, mean percentage of days on which rescue medications are needed, patient medication preference.

Statistical Considerations:

Sample Size: Sample size estimation was made referencing a trial evaluating GERD patients refractory to lansoprazole 30 mg daily. Patients in this trial were then randomized to treatment with lansoprazole twice daily or esomeprazole once daily. The mean percentage of GERD free days in the twice daily lansoprazole group was 57.5% (standard deviation 34.8%) (16). For the purposes of our trial with fexofenadine, we considered an additional 50% reduction in percentage of days with symptomatic GERD as a clinically significant endpoint (or mean percentage of GERD free days of 78.75%). Using alpha = 0.05 and beta 0.8 with paired means we calculated a needed sample size of 24 patients. *Our overall goal will be to recruit 40 patients to allow room for error.*
Data Analysis: We plan to analyze all data using a paired t-test comparing response to fexofenadine to response to placebo for each individual patient, provided data has a normal distribution. If not, then paired non-parametric analysis will be used. We will look specifically at the last week of treatment as we expect the drug to take a few days to build up to maximal effect. Drug preference will be compared using Fisher's exact test. Side effects will be compiled into a table to assess for major differences between fexofenadine and placebo.

Outline of key procedures/visits:

Recruitment:
Patients with potential proton pump refractory GERD will be contacted by phone or e-mail to assess interest, or recruited during office visits. Patients presenting to GI clinics will be pre-screened for potential recruitment. The decision to offer enrolment will be up to the treating physician. If the treating physician feels further workup or treatment is needed, then this should be done prior to initiation of the trial.

Patients will complete an intake questionnaire which will be e-mailed to them via RedCap or secure e-mail, or they will complete the form in person in the office. This intake questionnaire will be reviewed by study staff to determine eligibility to start the run-in period. Prior to run in a subject ID number will be assigned, starting with 1 and increasing sequentially. If a patient presents to an office visit, they will be consented at that time with signatures. If they are contacted by phone/e-mail, they will be provided with the consent form and explanation of the study, but formal consent and signing of the consent forms will take place after the run-in period if they are candidates to continue the study (the run-in week of the study involves no intervention other than questionnaires and is minimal risk).

Run in period (1 week):
1. Patient will take proton pump inhibitor as previously prescribed.
2. Every night before bed patient will record both the number and severity (on a scale of 0-4) of the reflux episodes during the last 24 hours, and need for rescue medications (patients can only use Tums during this trial) in a diary that we provide.

3. On the last day of the period patient will fill out a GERD-HRQL questionnaire about symptoms during the last week.

We will assess by either phone or secure e-mail the number of days on which the patient had symptoms. If the patient had enough symptoms he/she will be invited to participate and to visit the office to sign consent if this was not done at an earlier time. At this point a randomization ID number will be assigned.

Office visit or phone/e-mail conversation (needs to be an office visit if consent has not been signed):

1. Study materials will be collected thus far.
2. Randomization will occur and first drug will be distributed either in person or by mail.

First randomization period (2 weeks):

1. Patient will take proton pump inhibitor as previously prescribed.
2. Patient will also take the study drug (either fexofenadine or placebo) in the morning.
3. Every night before bed patient will record both the number and severity (on a scale of 0-4) of the reflux episodes during the last 24 hours, and need for rescue medications (patients can only use Tums during this trial) in a diary that we provide.
4. On the last day of this period patient will fill out a GERD-HRQL questionnaire about symptoms during the last week.
5. On the last day of this period patient write down any side effects potentially from the drug
6. On the last day of this period patients will say if they think they received placebo or active treatment

Washout (1 week):

1. Patient will take proton pump inhibitor as previously prescribed.
2. Every night before bed patient will record both the number and severity (on a scale of 0-4) of the reflux episodes during the last 24 hours, and need for rescue medications (patients can only use Tums during this trial) in a diary that we provide.
3. On the last day of the period patient will fill out a GERD-HRQL questionnaire about symptoms during the last week.

Crossover will occur and second drug will be shipped to the patient or distributed at the office. We will touch base with the patient either by phone/in the office/or by secure e-mail at this time.

Crossover (2 weeks):

1. Patient will take proton pump inhibitor as previously prescribed.
2. Patient will also take the opposite study drug as before (either fexofenadine or placebo) in the morning.
3. Every night before bed patient will record both the number and severity (on a scale of 0-4) of the reflux episodes during the last 24 hours, and need for rescue medications (patients can only use Tums during this trial) in a diary that we provide.
4. On the last day of this period patient will fill out a GERD-HRQL questionnaire about symptoms during the last week.
5. On the last day of this period patient write down any side effects potentially from the drug.
6. On the last day of this period patients will say if they think they received placebo or active treatment
7. On the last day of this period patient will select which drug was most effective.

Office visit or phone/e-mail conversation:

1. Study materials will be collected or mailed/e-mailed to us by the patient.
2. We will ask the patient either in person or by e-mail if they have questions and check in on how they are doing from a medical standpoint.

Drug Acquisition, Storage, and Distribution:

- Drugs will be ordered in batches of 300 from Koshland pharmacy (301 Folsom St B, San Francisco, CA 94105, e-mail info@koshlandpharm.org, contact Peter Koshland). The capsules will look identical.
- There will be an un-blinded person (George Triadafilopoulos) who distributes the capsules (14 each) into bottles labeled with a code 1 or 2, which corresponds to fexofenadine or placebo. The bottles will also be labeled with subject number.
- Drugs will be stored at room temperature in a locked cabinet. Storage life is 6 months.
- During distribution a different staff member will distribute the drugs based on a randomization code that contains the subject ID number and the order of the drugs the patient will receive.
- After distribution, on the same randomization sheet the staff member will fill in the patient name, and date the drug is distributed. This will be stored in the same locked cabinet as the drugs.
- The randomization code will be kept by George Triadafilopoulos
- We will not be perusing an IND, please see below
    - The IND Regulations [21 CFR 312.2(b)] state that clinical investigation of a drug product is exempt from the requirements for an IND if all of the following apply:

        - The Drug used in the investigation is lawfully marketed in the United States.
        - The investigation is not intended to be reported to FDA in support of new indication for use or to support any other significant change in the labeling for the drug.
        - The investigation is not intended to support a significant change in the advertising of the product.
        - The investigation does not involve a route of administration or dosage level, use in a participant population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
        - The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50].
        - The investigation is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR part 312.7], e.g., the drug may not be represented as safe or effective for the purposes for which it is under investigation, nor may it be commercially distributed or sold.

Withdrawal from the study:

- Patients can be withdrawn for the following reasons
    - Side effect possibly related to the study drug
    - Failed adherence to study protocol
    - Discovery that the patient no longer meets inclusion or exclusion criteria
    - Other reasons after discussion with the other investigators

Safety Data:

The side effects of fexofenadine are minimal and similar to placebo (14, 15). Some side effects that occurred similarly in both the placebo and fexofenadine group include headache, dizziness, upper respiratory tract infection, pharyngitis, rhinitis, sinusitis, nausea, dyspnea, diarrhea, and pain. Patients will be asked to list side effects at the end of each treatment period.

Expected Results:

We suspect the majority of PPI refractory patients in our study will have a component of visceral hypersensitivity given the efficacy of PPIs in reducing acid secretion. Based on prior studies showing efficacy of H1 blockers in IBS, we suspect a similar mechanism will be at play in the esophagus to reduce the sensation of GERD.

Limitations:

This is a small-scale trial and is lacking of pH/impedance data which would better help elucidate the mechanism of GERD. However, such testing would greatly increase cost and reduce patient interest in study participation.

Future Directions:

If positive, future directions include potential collaborations with industry and potential larger scale and longer trials to bring either fexofenadine or similar drugs to market for more widespread use.

Proposed Timeline:

January-February 2018: IRB approval (IRB-44650)
February-December 2018: Recruitment and clinical trial
Jan-February 2019: Data-analysis and manuscript preparation

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