Placebo Controlled Trial of Metoprolol in CHF patients with reactive airways

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A. Study Purpose and Rationale

The purpose of this study is to demonstrate a survival benefit for asthatic/COPD CHF patients with metoprolol, a beta-1 antagonist. The morbidity and mortality benefit of beta-blockers for patients with CHF has been well established in multiple large multi-center controlled trials. These trials exclude COPD/asthma patients because of the concern for bronchospasm that is associated with beta-blockers. Thus, the possible benefit to COPD patients is unknown.

The beta blocker trials include CIBIS II trial which included 2647 patients. It showed a reduction in all cause mortality in bisprolol treated class III and IV CHF patients from 17.3% to 11.8% compared with placebo. This corresponds to annual mortality rate of 13.2 and 8.8% respectively. In addition to mortality benefit hospitalization was reduced by 20%.

The MERIT-HF trial evaluated metoprolol given to patients with CHF diagnosed by decreased LVEF and symptoms of heart failure. This trial recruited 4000 class II-IV multiple etiology CHF patients. This trial showed a 34% risk reduction for beta-blocker treatment. The annual mortality rate in the treatment arm was 7.2% compared with 11% in the placebo arm.

Thus, the survival benefit to CHF patients in these studies is dramatic. However, patients with COPD were excluded from these studies since bronchospasm can be initiated with beta blockade. Due to this, clinicians have been reluctant to initiate beta-blocker treatment in asthma/COPD patients because the benefit is not known and there is concern that the pulmonary disease may be exacerbated. Thus, a study is needed to show that beta blockade is safe and effective in patients with COPD.

Most beta-blockers are non-selective and interact with both beta-1 and beta-2 receptors. The beta-1 receptors are cardiac whereas the beta-2 receptors are pulmonary. Metoprolol is a beta-1 antagonist; therefore, it is less bronchospastic than nonspecific beta blockade. Metoprolol has been tested in asthma/COPD patients since it can also be used for blood pressure control in patients with COPD/asthma. Beta-1 antagonists are generally well tolerated, however, in some patients they cause wheezing and should be discontinued. This bronchospasm, if clinically significant, can be reversed with an inhaled beta agonist.

FVC, FEV1, and PEF have been shown to decrease with metoprolol treatment, however studies show no clinically apparent respiratory effects with metoprolol despite these changes in pulmonary function testing. Any bronchospasm is reversed with an inhaled beta agonist such as salbutamol or terbutaline. Studies of the effect of metoprolol vs. placebo on asthmatics have been done, since metoprolol is also used for hypertension, although it is not used as first or second line therapy for blood pressure control in COPD patients.

Lawrence showed that 14 asthmatics tolerated metoprolol 100 mg bid when given with salbutamol over the short and long (3 weeks) term, despite the change in PFTs. Similarly, Lammers showed in 8 mild-moderate asthmatics that Metoprolol 100 mg will cause decrease in PEFR two hours after dosing which is reversed with terbutaline inhalation. Metoprolol use was not associated with symptoms of dyspnea. Tantucci showed the same results in 12 asthmatics. Metoprolol CR at doses of 100-200 mg/day has been shown by Lofdahl in 8 asthmatic hypertensives to be well tolerated. However, one patient did experience an asthma exacerbation and was withdrawn. Of note, no concomitant inhaled beta agonist was used in this study. Bauer showed that 18 hypertensive asthmatics could tolerate metoprolol given with salbutamol at the anticipated peak plasma concentration time. After one and seven days the PFTs did not change.

In sum, metoprolol has been shown to be relatively safe in patients with bronchial hyperresponsiveness and that terbutaline or salbutamol can reverse the bronchospasm if it occurs. The potential benefit of beta blockade in patients with COPD and CHF merits a trial to test this hypothesis. Such a trial would enable an evidence based treatment plan in these CHF patients who currently are generally denied beta-blocker therapy.

B. Study Design and Statistical Analysis

The study will require a total of 464 patients who will be randomly assigned to metoprolol or to placebo in a double-blinded study. The treatment group and control group each involves 232 patients with CHF and COPD/asthma. These patients will then be followed for three years with the primary endpoint being all cause mortality. This number is based on a power of 80% and a p value of 0.05 for detecting a difference of 12%. This is based on the MERIT trial, which determined the annual mortality rate to be 7% in the treatment group, compared with 11% in the placebo group, thus three year mortality would be 21% and 33% respectively.

In addition, the number of all cause hospitalizations as well as the number of COPD exacerbations will be followed as secondary endpoints. It will be interesting to see if there is any long-term COPD effect. It is expected that hospitalizations will be fewer in the treatment arm and that COPD exacerbation number, as defined by requiring a steroid taper, should be equivalent. Some patients may not tolerate metoprolol/placebo secondary to bronchospasm. Such patients shall be withdrawn from medication but included in their original group for data analysis purposes in an intention to treat analysis. There will be no cross over allowed.

The method of data analysis will be a chi-squared statistical analysis of the mortality rate in the placebo compared with the control group. The secondary endpoints of hospitalization and COPD exacerbations will be analyzed using a t-test.

C. Study Procedures

Patients noted to have both CHF and COPD will be recruited and consented if their clinicians first agree to participate in the trial. They will fill out a questionnaire regarding the current severity of their CHF and COPD at the start of the study. The patient will be followed for two years and asked to report any COPD exacerbations or hospitalization. Patients will be followed by their regular clinicians, who will initiate therapy with oral metoprolol or placebo and monitor patients COPD and CHF as per their routine. This will be initiated with an inhaled beta agonist, if the patient is not already on this medication. The patient will remain in the waiting room in the first three hours after the first dose to ensure no adverse affect. If wheezing occurs an inhaled beta agonist and/or theophylline will be initiated and the therapy will be withdrawn. Patients, who tolerate metoprolol, will be titrated up in dose slowly to the maximum tolerated dose of up to 200 mg per day, as per the Merit study protocol. This means starting at a dose of Metoprolol CR/XL 12.5-25 mg/day increased every two weeks as tolerated. Any later adverse reaction will cause the dose to be decreased to the last tolerated dosing. Any pulmonary function testing or cardiac procedures will be performed at the discretion of the patient and their practitioner.

D. Study Drugs

Metoprolol is a prescription medication. This drug was chosen because it has been shown to improve survival in heart failure patients. Metoprolol was also chosen because it has shown to effectively decrease heart rate and blood pressure without causing significant wheezing in patients with reactive airways. In addition, the pulmonary effects of decreased FEV and PEF are reversible if necessary thus this medication can be safely administered and the possible respiratory effects can be reversed and will be evident following the first dose in the doctor's office if they occur. In addition the primary physician will administer an inhaled beta agonist simultaneously. Metoprolol will be administered in the usual oral route

using the usual hypertension/CHF dosing of 25-200 mg per day. The most common side effects of Metoprolol as noted in the PDR are as follows.

Tiredness and dizziness in 10% of patients. Depression in 5%. Short-term memory loss, mental confusion, headache, somnolence, nightmares and insomnia have been reported. 3% may experience dyspnea and bradycardia. 1% may experience cold extremities, arterial insufficiency, palpitations, CHF, peripheral edema, syncope, chest pain and hypotension. 1% may experience bronchospasm and dyspnea. Diarrhea has been reported in 5%, 1% complain of nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn. 5% may experience pruritis or rash.

E. Medical Devices

None.

F. Study Questionnaires

The questionnaire will identify patient's age, race, sex, socioeconomic class, heart failure class, degree of respiratory dysfunction and tobacco/alcohol history.

G. Study Subjects

General Characteristics: Patients are to be enrolled over a 3-6 month period. Eligible patients are men and women age 40-80 with CHF for 3 months or more. Exclusion: diabetes, significant renal /hepatic/CNS impairment i.e. AST>3times normal, Cr>250 umol/L, pregnancy, lactation, known severe adverse reaction to beta-blocker. Acute illness. Current beta-blocker use.

Cardiac Characteristics: Diastolic BP >90 mm Hg, Systolic BP>100 mm Hg, LVEF<40% by echo or radionucleotide scan. NY Heart Association functional classes II-IV with symptomatic CHF for at least 3 months prior to randomization. Patients should be on optimum standard therapy including ace-inhibitor or angiotensin II blocker and diuretic. Exclude: second/third degree heart block, HR <50, sick sinus syndrome, MI/unstable angina/CABG/coronary angioplasty in previous one month. Primary valvular or myocardial disease, amiodorone use within 6 months. Unstable decompensated heart failure (pulmonary edema/hypoperfusion), calcium blocker use.

Ventilatory Characteristics: FEV1 >50% predicted, increase in FEV1 of >/= 15% with beta-blocker by MDI, normal chest X-ray. Stable asthma regimen including bronchodilator and inhaled corticosteroids. Exclusion criteria: FEV1 <50% predicted, exacerbation of COPD within 6 weeks prior to start of study, current oral steroid use.

H. Recruitment of Subjects

The individuals will be recruited from the pulmonary function lab where 230 patients are seen per month. Of these 50% have COPD and of those 10% have CHF. Thus, this database can be used to identify potential subjects in the last five years using the computer database (690 patients). First the patient's physician will be contacted and informed of the purpose of the study. If the physician consents to the study, the patient will then be contacted and consented to participate in the study.

I. Confidentiality of Study Data

Patients will be coded by # of entry. The patient information will be stored in a locked office accessible only to investigators. Patient's name, number and medical information will not be divulged without the explicit written permission of the patient.

J. Potential Conflict of Interest

None

K. Location of Study

The NY Presbyterian Hospital.

L. Potential Risks

Bronchospasm, dizziness, dyspnea, bradycardia, CHF exacerbation, hypotension and any other side effects reported with metoprolol, which are rare.

M. Potential Benefits

A relative risk of 0.66 for mortality in the treatment group. Improvement in CHF symptoms. Augmentation of heart function. Decreased hospitalization.

N. Alternative therapies

CHF survival can also occur with ACE-I and Spironolactone. The RALES study showed a reduction of mortality from 46 to 35% with Spironolactone. The SOLVD trial showed an 8% mortality reduction with ACE-I. These benefits are aside from the added benefit of beta-blockers for CHF.

O. Compensation to Subjects

None.

P. Costs to Subjects

None, medication will be provided by the study.

Q. Minors as Research Subjects

None.

R. Radiation or Radioactive Substances

None.

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