The Effect of a Leukotriene Receptor Antagonist, Montelukast, in the Emergency Room Management of Acute Asthma

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A. Study Purpose and Rationale

Asthma is a chronic respiratory disease characterized by reversible airway obstruction, increased airway responsiveness to a variety of stimuli, and airway inflammation. Asthma episodes involve progressively worsening shortness of breath, cough, wheezing or chest tightness, or some combination of the above. It is a heterogeneous condition that affects 5-10% of the US population.[1] Despite the increased understanding of the underlying pathophysiology and the availability of improved and effective therapeutic agents the prevalence of this disease in the US continues to increase causing significant morbidity and mortality.[1,2,3] It has been estimated that there are 1.8 million emergency room visits for acute asthma exacerbations in the US annually.[1,2] Many investigators have studied various components of the assessment and treatment of acute attacks and some important guidelines have been delineated including, the aerosolized use of sympathomimetics and assessing objective measurements of airflow obstruction.[4] Corticosteroids, which modulate the associated inflammation, have been shown to prevent relapses of bronchospasm and are frequently administered in the emergency room setting.[5] Given that there is a lag period from 6 to 12 hours before steroids can produce an effect, more controversy surrounds there use early in an exacerbation to influence duration of the attack and hospital admission rates.[6,7]

A more recent advancement in the treatment of asthma was the introduction of a new class of agents, the leukotriene inhibitors. Leukotrienes are the end product of arachidonic acid metabolism which is formed when phospholipids are cleaved from cell membranes. Arachidonic acid is then metabolized by several pathways including the cyclooxygenase and the 5-lipoxygenase pathways. It is the 5-lipoxygenase pathway that produces the leukotrienes. Of those produced, leukotriene B4 is a potent chemoattractant for neutrophils and eosinophilS.[8-9,10] Leukotrienes C4, D4, E4 , the cysteinyl leukotrienes, which exert their effects through a common receptor, are potent bronchoconstrictors that enhance bronchial permeability and decrease mucocilliary clearance.[8,9,10] Studies in humans have implicated leukotrienes as a key mediator in the pathogenesis of asthma. They have demonstrated that inhalation of leukotrienes can reproduce features of asthma such as bronchoconstriction, airway hyperreactivity, and inflammatory cell influx.[8-9,10] Leukotrienes are found in increased amounts in the bronchoalveolar lavage fluid and urine during asthma exacerbations and are produced by mast cells and eosinophils, important inflammatory cells in the pathogenesis of asthma.[10] Once the role of leukotrienes was elucidated, further work was done to develop approaches to modify or inhibit their activity. Two main classes of -leukotriene inhibitors have been developed, the 5-lipoxygenase inhibitors and the leukotriene receptor antagonists. Many randomized, placebo-controlled studies have demonstrated their efficacy in the treatment of asthma.[11,12,13] They may now be used in addition to inhaled corticosteriods and B-agonists in the chronic treatment of asthma. Interestingly, several studies have shown that these agents may also have a more immediate affect in the acute management of asthma. Gaddy et. al., in 1992, used a leukotriene D4 receptor antagonist, MK-571, administered intravenously and demonstrated that within twenty minutes there was an increase in FEV1 of over 20%.[14] An oral 5-lipoxygenase agent has also been shown to produce acute brochodilitation with improvements in FEVI within I to 4 hours after ingestion.12 This study will investigate a new, orally administered leukotriene receptor inhibitor, Montelukast, in the emergency room management of acute asthma. Studies have demonstrated the efficacy of Montelukast for the chronic treatment of adolescents and adults with asthma.[16,17,18] One smaller study (n=12) showed that doses of 5 mg can inhibit early and late phase bronchoconstriction due to antigen challenge by 75% and 50% respectively.[19] Doses of 100mg and 200mg were administered to 22 people with chronic asthma and were

shown to cause significant bronchodilitation within one hour.[15] This proposed study will look at the early administration of Montelukast in acute asthma and the change in peak expiratory flow rates and the rate of hospital admissions from the emergency room.

B. Study Design and Statistical Analysis

The study planned is to be a randomized, double-blind, placebo controlled trial of patients from 18 to 45 years of age presenting to the emergency room for treatment of acute asthma. Exclusion criteria are those patients who are pregnant or who have another medical condition including sickle cell disease, cancer, heart disease, liver disease, or acquired immunodeficiency syndrome. Those who are taking a leukotriene inhibitor as maintenence therapy for their asthma wiH be excluded. In addition, patients whose respiratory distress inhibits them from taking an oral medication or signing an informed consent will also be excluded.

On arrival to the emergency room all patients will be given the standard therapy of nebulized aerosol containing albuterol sulfate inhalation solution (2.5mg/3ml). Within thirty minutes of presentation patients will be approached by an investigator or by a medical house officer for recruitment into the study. Patients who meet inclusion criteria and sign an informed consent will be randomly assigned to either receive Montelukast 10mg (two 5 mg chewable tablets) or placebo. Randomization and drug preparation will be done by emergency room physicians not involved in the patient recruitment. On entry, patient variables such as severity of bronchospasm (as characterized by the patient using a scale from 0 to 3 corresponding to none, mild, moderate, or severe as previously described [6,7], recent(within past 48 hours) presentations to the emergency room and oral steroid use for the treatment of asthma exacerbations, hospitalizations for asthma within the prior six month period, and current cigarette smoking wiH be recorded. Temperature, heart rate, respiratory rate, and oxygen saturation on room air will be noted on presentation.

Patients will continue to receive nebulized B-agonist treatments at regular intervals until admission to the hospital or discharge home. The administration of additional medications including corticosteriods will be at the discretion of the treating physician. Peak expiratory flow rates will be determined by a mini-Wright flow meter on presentation to the emergency room, on entry to the study, and at one hour intervals thereafter. Three PEF measurements will be taken at each interval with the highest value recorded. The time of presentation, of entry into the study, and of discharge or admission will be recorded. The decision to admit or discharge a patient will be made by a physician without knowledge of previous patient group allocation.

Prior studies have shown the hospital admission rates for asthma to be approximately. 15%. Therefore, in order to appreciate a 30% difference between treatment groups, sample size was calculated to be 3558 with a power of 80%. Changes in PEF were evaluated using analysis of covariance with treatment group as the independant variable and disposition(admission or discharge) as the covariate.

C. Study Procedures

Patients will be enrolled in the study from presentation to the emergency room until admission to the hospital or discharge home has been decided. They will undergo measurement of peak expiratory flow rates which requires the patient to deliver a rapid expiratory breath through a mini-Wright flow meter at presentation, at 30 minutes, and every hour for the duration of the study period. This may represent more frequent measurements than clinically indicated.

D. Study Drugs

Montelukast is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene receptor. It is approved for the prophylaxis and chronic treatment of asthma in adults and pediatric patients age 6 and older. It will be given orally at the standard 10mg dose. Tolerability data

are available from 1955 adult patients who participated in placebo controlled clinical trials evaluating Montelukast at a dosage of 10mg/day.[17] The most common adverse side effect was headache(18.4% of Montelukast vs. 18.1% of placebo). Others included cough and abdominal pain with rates comparable to placebo 2.7% vs.2.4% and 2.9% vs. 2.5% respectively.[17]

E. Medical Devices

Not Applicable

F. Study Questionnaires

Not Applicable

G. Study Subjects

Men and women ages 18 to 45 presenting to the emergency room with acute asthma will be included in this study. Exclusion criteria include active pregnancy or an underlying medical condition such as heart disease, sickle cell disease, HIV, or cancer. Patients whose respiratory condition is to severe to administer oral medication will also be excluded as will patients currently taking a leukotriene inhibitor.

H. Recruitment of Subjects

Patients will be identified on arrival to the emergency room.

I. Confidentiality of Study Data

All study data will be coded with a unique number for each subject and kept in a secure location.

J. Potential conflict of Interest

Neither the investigators nor the University has a proprietary interest in the drug under investigation.

K. Location of the Study

Columbia Presbyterian emergency room.

L. Potential Risks

These include the reported side effects of Montelukast, including headache, abdominal pain, and cough. Hypersensitivity reactions may occur to some component of the medication.

M. Potential Benefits

The potential benefit may be a more rapid improvement in the symptoms of acute asthma and a decreased need for hospitalization. In addition, this study may provide some insight into additional methods of approaching asthma in the acute setting.

N. Alternative Therapies

All patients would receive B-agonist nebulizer treatments. Additional therapies and admission to the hospital will be decided by the treating physician as indicated by the disease severity.

O. Compensation to Subjects

There is no compensation to subjects for this study.

P. Costs to Subjects

There is no cost to subjects for their participation in this study.

Q. Radiation or Radioactive Substances

Not Applicable

R. Minors as Research Subjects

Not Applicable

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