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Comparing peak oxygen consumption following administration of albuterol vs Levalbuterol

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A. Abstract

Asthma is a pulmonary disease characterized by reversible airway obstruction and inflammation affecting 7 million children in the United States. It is a highly prevalent condition and the most common medical emergency in pediatrics. β 2 agonists remain the mainstay of pharmacotherapy in asthma. β 2 selective agonists are desirable to avoid the non-selective α and β 1 receptor stimulation which may cause adverse effects. Albuterol (β 2 agonist) remains the most commonly used bronchodilator in asthma and patients with chronic lung disease. Albuterol is a 50:50 mixture of R albuterol (levalbuterol) the active moiety responsible for the bronchodilatory effect and S albuterol. S albuterol was earlier thought to be an inactive isomer however recent studies suggest otherwise. Evidence from pre-clinical studies suggests that the S enantiomer has brochoconstricting and pro inflammatory properties and is metabolized 12 times slower than the R isomer which results in higher circulating levels of the S enantiomer as compared to the active R enantiomer following administration of racemic albuterol. However cardiovascular adverse effects remain the main dose-limiting factor for β2 selective agent usage namely tachycardia, diastolic hypotension, arrhythmias and other side effects include skeletal muscle tremor and nausea. We propose that the underlying mechanism for these effects is due to increased oxygen consumption caused by the racemic albuterol as shown in animal studies specifically the S enantiomer. Previous Rhesus monkey studies performed by our group have shown that racemic albuterol increases the oxygen consumption by 46.5% from baseline compared to a 10% increase after administration of levalbuterol. To date there are no human studies that have measured the change in oxygen consumption following administration of levalbuterol.

B. Background

Albuterol a β2-adrenoreceptor agonist was first marketed in 1968 known for its brochodilatory action. Albuterol contains a racemic mixture of two enantiomers namely the R(active form) and the L(considered inert) form. Some of the side effects of the racemic albuterol include jitteriness, anxiety and palpitations. Levalbuterol contains the single enantiomer (R – form) and is preferred in instances where the tachycardia caused by the racemate may be detrimental to the overall clinical status of the patient. However there are no studies to date that have elucidated the potential cause of the tachycardia in patients receiving albuterol attributed mainly to its β2 receptor agonist function.

Field et al[1] measured the cost of breathing in 13 patients on mechanical ventilation as the difference between the oxygen consumption during spontaneous respiration and that during mechanical ventilation and found that the oxygen cost of breathing increases from less than 5 % of total VO2 (oxygen consumption) in a normal resting spontaneously breathing patient to a range of 8 -24 % of total VO2 on mechanical ventilation. Patients with cardiorespiratory or lung diseases have been shown to have elevated oxygen consumption while mechanically ventilated. β agonists can increase the oxygen consumption either by increasing minute ventilation through stimulation of the respiratory center or by directly stimulating the respiratory muscles. Furthermore there are no studies that have measured the change in oxygen consumption following administration of levalbuterol. Oxygen consumption increases in diseases states such as fever, sepsis and trauma and leads to an increased metabolic demand. Increase in oxygen consumption that is disparate to the oxygen delivery leads to anaerobic metabolism and lactic acidosis and can further worsen the clinical status or delay recovery. Also there may be impaired oxygen extraction or use at the cellular level i.e. cytopathic hypoxia thus creating a functional arteriovenous shunt. Maintaining adequate oxygen delivery to meet the metabolic demands is fundamental in treating critically ill patients.

A double blind placebo controlled trial studied pharmacokinetics of albuterol and its enantiomers and showed that, in fact the S enantiomer does not have any effects on extra pulmonary β 2 receptors. However the S enantiomer does not exert its effects through the β 2 receptor. Henderson et al[2] studied the clinical effects of the two enantiomers on mouse models and showed that the R enantiomer of albuterol increases airway edema and bronchial responsiveness in response to a methacholine challenge which provokes bronchoconstriction whereas the S enantiomer had the opposite effects. These bronchocontrictor and proinflammatory effects of the S enantiomer may gradually overcome the bronchodilatory effects of the R enantiomer in the racemate and that R enantiomer balances the bronchospastic effects of the S enantiomer in the racemate. There are studies suggesting the differential effects of the two enantiomers.

Newth et al[3] in 1990 reported changes in minute ventilation and oxygen consumption in 10 anesthetized intubated rhesus monkeys in response to multiple B agonists. The study revealed that of the multiple β agonists (salmeterol, formoterol, fenoterol, salbutamol) along with comparison to normal saline and theophylline, the most profound effects on oxygen consumption were after administration of inhaled racemic albuterol. Racemic albuterol increased the oxygen consumption (VO2) by 46.5% over control ($P < 0.001$). Other variables such as heart rate, respiratory rate and minute ventilation also showed an increase of 60.2 %, 51.9% and 82.8% respectively. As the article stated, in patients with cardiorespiratory disease and with low reserve, the potential for hypoxemia will depend on the change in oxygen extraction and pulmonary vasculature and whether the cardiac

output can be increased to match the demand and if the extent of bronchodilation can increase ventilation to a degree that can sufficiently offset the increase in oxygen consumption.

In a follow up study by Newth et al[4] in 1997 studied the effects of Bronchodilators on Spontaneous Ventilation and Oxygen Consumption in anesthetized intubated Rhesus Monkeys showed that racemic albuterol) caused an increase in Oxygen consumption of 45% and minute ventilation of 50%. These changes were suppressed in the presence of a β blocker such as propranolol. Therefore the increase in oxygen consumption could be secondary to β adrenoreceptor stimulation resulting in stimulation of the respiratory center or due to increased metabolic demands.

β agonists are used extensively in pediatric patients with chronic lung disease, asthma or for its mucolytic property. Many of these children are admitted primarily for another condition for example septic shock, in which case their oxygen demands may already be increased. In such conditions administering β agonists that may further increase oxygen consumption and oxygen costs of the body may be have deleterious effects on the overall clinical status of the patient.

C. Hypothesis: Levalbuterol does not increase oxygen consumption to an extent that is increased by salbutamol (albuterol).

D. Purpose of this Study: The purpose of our study is to study the peak oxygen consumption in subjects scheduled to receive albuterol and compare it with that of levalbuterol using a non-invasive method with the Innovision Innocor machine. To date, no known human studies that have measured the change in oxygen consumption after levalbuterol.

1. Study Objectives

Primary objective is to measure the peak oxygen consumption at baseline and then after the administration of albuterol and levalbuterol inhalation in patients admitted to or currently cared for in the pediatric intensive care unit (PICU) or cardiothoracic intensive care unit (CTICU) at Children's Hospital Los Angeles with asthma reactive airway or chronic lung disease.

Secondary objectives are to collect change in Cardiac output, systemic vascular resistance, stroke volume, minute ventilation, heart rate, blood pressure, respiratory rate, pulse oximetry with each intervention.

E. Significance and preliminary studies

Albuterol has been in used in the treatment of asthma to relieve bronchospasm for nearly 45 years. However numerous reports have associated long term use of racemic albuterol with increasing morbidity and mortality. Mechanisms underlying these observations are not well known at this point.

Recent studies have shown that the S enantiomer has bronchoconstricting and pro-inflammatory properties which may be counterbalanced by the R enantiomer in the racemate. Numerous studies have been reported to question the clinical efficacy of racemic albuterol or in fact that the racemate may actually have deleterious effects on the bronchioles. Racemic albuterol consists of 50% each of the active and the inactive isoform. However there is accumulating body of data from animal studies questioning the inactive or rather the counteractive nature of the S isoform.

Although β 2 agonists have been in use for a long time, controversies exist as to their efficacy and safety over long term use. Animal studies focusing on the long term use of racemic albuterol have shown that it increased airway hyper responsiveness, edema and susceptibility to spasmogens. These effects have been understood to be from the S isoform as previous clinical trials have demonstrated the individual bronchodilator properties of the R isoform along with suppression of pro inflammatory mediators.

Mazzoni et al[5] have reported that bronchospasm in sensitized animals was completely suppressed by an infusion of racemic albuterol, however a more prolonged infusion longer than 1 hour increased their susceptibility to the antigen and induced hyper responsiveness to histamine. This progressive loss of efficacy of racemic albuterol with time is speculated to be from disproportionate accumulation of the S enantiomer due to stereospecific metabolism of the R enantiomer.

A randomized controlled trial was conducted by Wraight et al[6] to study the adverse effects on lung function by short acting β agonists. The study included 36 subjects with mild to moderate asthma on racemic albuterol along with inhaled corticosteroids. Subjects were randomized to two groups, one receiving a combination of albuterol and ipratropium and the other receiving ipratropium alone. The study consisted of two phases. FEV1 measurements were done while on these medications during phase 1 and inhaled corticosteroids were then withdrawn during phase 2 and changes in FEV 1 and FEV1 % were recorded following the withdrawal. The results showed that there was a significant loss in lung function as evidenced by drop in FEV 1 in patients with mild to moderate asthma as compared to those on ipratropium. Furthermore when inhaled corticosteroids were discontinued there was a larger fall in FEV 1 in the β agonist group compared with the ipratropium group. These data suggest that in poorly controlled asthma wherein patients are taking short acting agonists frequently the adverse effects may be more pronounced especially when the anti-inflammatory effects of the inhaled corticosteroids are absent.

F. Research Design and Methods

Study Overview

This is a single center prospective randomized controlled open label cross over study in the 24 bed multidisciplinary medical-surgical Pediatric Intensive Care Unit (PICU) and 22 bed multidisciplinary Cardio-Thoracic Intensive Care Unit (CTICU) at Children's Hospital Los Angeles.

a. Eligibility & Recruitment

This will be a single center prospective randomized open label cross over study. There will be three cohorts of subjects.

1. Intubated patients receiving Albuterol
2. Non–intubated patients receiving albuterol who are cognitively able to obtain measurements with a mouthpiece
3. Healthy adult volunteers

a. Subject Eligibility – Intubated and non-intubated patients

For intubated patients all subjects 1 month to 17 years of age admitted to the pediatric intensive care unit (PICU) or cardiothoracic intensive care unit (CTICU) will be screened throughout their stay for inclusion. For non-intubated patients all subjects 1 month to 21 years old admitted to the pediatric intensive care unit (PICU) or cardiothoracic intensive care unit (CTICU) will be screened throughout their stay for inclusion. Particular subject eligibility will be based on the following inclusion and exclusion criteria.

b. Inclusion Criteria

For intubated patients: any patient 1 month to 17 years old admitted to the pediatric intensive care unit (PICU) or cardiothoracic intensive care unit (CTICU) with asthma, reactive airways or chronic lung disease and is scheduled to receive albuterol or levalbuterol.

For non-intubated patients: any patient 1 month to 21 years old admitted to the pediatric intensive care unit (PICU) or cardiothoracic intensive care unit (CTICU) with asthma, reactive airways or chronic lung disease and is scheduled to receive albuterol or levalbuterol.

c. Exclusion Criteria

1. If intubated, patients with a large endotracheal tube leak (greater than 18%)

2. SpO2 less than 95 % while receiving an FiO2 of > 40%, signifying intrapulmonary shunting in which case the use of albuterol or L-albuterol coud change the degree of intrapulmonary shunt during the testing.

a. Subject Eligibility – Healthy Volunteers

Healthy volunteers less than 60 years of age available to participate on two consecutive days

b. Inclusion Criteria – Healthy volunteers less than 60 years of age

c. Exclusion Criteria – Any contraindication to use of Albuterol such as known allergy to albuterol or levalbuterol.

Protocol for intubated and non-intubated patients receiving albuterol or levalbuterol
After obtaining a written informed consent from patients/guardians that are scheduled to receive albuterol or levalbuterol, the subjects will be randomized using pre-prepared opaque sealed envelopes to two different groups, group A and B. The measurements will be done over 2 separate days. On Day 1 Group A will receive albuterol first followed by levalbuterol for when the next dose is due. On day 2 the order will be reversed and therefore levalbuterol will be given first followed by albuterol. Group B will be first given levalbuterol followed by albuterol for the next scheduled dose. If the patient is receiving albuterol as their clinically prescribed medication the levalbuterol dose will be chosen to be ½ that milligram amount. If the patient is receiving levalbuterol as their clinically prescribed medication the albuterol dose will be chosen to be 2 times that milligram amount. Typical dosages in the ICU would be albuterol 0.15 mg/kg with a minimum of 2.5 mg and maximum of 5 mg and levalbuterol 0.63 mg and 1.25 mg respectively. However, if a young child is clinically prescribed a dose of Albuterol of 1.25 mg(max dose of levalbuterol) then the dose of Levalbuterol for the study would be 0.63 mg. Albuterol is only FDA approved for marketing to patients greater than 2 years of age but it has been used clinically at all age levels. Likewise, Levalbuterol has been used clinically in infants and children but is only FDA approved for marketing to patients greater than 6 years of age. Measurements of oxygen consumption will be done using the non-invasive device Innocor. This device has been validated for measurement of oxygen consumption against the gold standard Douglas bag. Oxygen consumption will be measured at baseline and then after giving albuterol and levalbuterol at times 0, 5 min, 10, 20, 40 and 60 minutes. The two medications will be given at least 4 hours apart.

The Innocor device has the ability to measure cardiac output by mixing in small amounts of Nitrous Oxide (N_2O) and Sulfur Hexafluoride 6 (SF_6). Oxygen consumption is measured by the Innocor device without the addition of these gases. For this study N_2O and SF_6 will not be used. No part of the Innocor device will be attached to the skin for the purposes of this research. The Innocor device can be used to measure pulmonary function tests requiring some degree of cooperation from subjects. It is possible to obtain measurements of oxygen consumption using the Innocor device in intubated, sedated patients without their cooperation. For non-intubated patients, they would only need to be able to follow the direction to breathe out through the sensor. No timing of breaths are required.

Protocol for Healthy Adult Volunteers
After obtaining a written informed consent from the volunteer, the subject will be randomized using pre-prepared opaque sealed envelopes to which medication (albuterol or levalbuterol) they receive first. The measurements will be obtained over 2 consecutive days. The dosage of

Albuterol will be 5 mg mixed with 2 to 3 ml of saline and will be aerosolized over 10 minutes. The dosage of levalbuterol will be 1.25 mg mixed with 2 to 3 ml of saline and will be aerosolized over 10 minutes. One day 1 of the study the patient will receive the medication they were randomized to. At approximately the same time of day on day 2 the subject will receive the other medication. Following each breathing treatment, oxygen consumption will be measured using the non-invasive Innocor machine. Oxygen consumption will be measured at baseline and then following the medication at times 0, 5 min, 10, 20, 40 and 60 minutes. Temperature will be measured prior to the aerosolized medication and heart rate, blood pressure, oxygen saturations, and respiratory rate will be measured at intervals over the 60 minutes of oxygen consumption measurement.

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$VO2 = (CO \times CA) - (CO \times CV)$
VO2 = Oxygen consumption
CO = Cardiac Output
CA = Oxygen concentration of arterial blood
CV = Oxygen concentration of mixed venous blood

Innocor is a non-invasive device that measures hemodynamic and gas exchange parameters for diagnostic purposes using the inert gas rebreathing technique and breath-by-breath analysis. The patient breaths through a mouthpiece or a facemask connected to the flow meter via a bacterial filter. A gas sampling tube is connected to the breathing assembly for side stream gas analysis. Carbon dioxide is measured continuously and simultaneously at the mouthpiece by a photoacoustic gas analyzer. Oxygen is measured by means of a laser diode absorption spectrometer.

The breath-by-breath method is the fastest responding of the non-invasive gas exchange methods for determination of the various gas exchange parameters such as oxygen uptake and carbon dioxide excretion. The Breath-by-Breath (BBB) Option provides measurements of metabolic gas exchange parameters by simultaneous measurements of the respiratory flow and gas concentrations when breathing ambient air. The respiratory flow is measured by means of a differential pressure type flow meter (pneumotachometer) placed between the respiratory valve unit and the patient. The principle in the determination of the oxygen consumption and the carbon dioxide excretion is to estimate the difference between airway influx and efflux of oxygen and carbon dioxide during inspiration and expiration. This is done by integrating the product of oxygen or carbon dioxide concentration and flow in the respiratory gas over an interval, which covers a complete respiratory cycle.

The gold standard for measuring respiratory exchange is the Douglas bag technique. Sheth et al[7] studied the correlation of VO2 obtained by Innocor with the Douglas bag technique. 31 children (ages 7 -17 years) were recruited for the study. A strong correlation was found between the two methods (R 2 0.82) The average discrepancy between the Innocor and the Douglas bag methods was 5.4% (range 0.1 – 32.2%). The Innocor provides a rapid mode of testing VO 2 as compared to the gold standard Douglas bag that involves collecting large volumes of expired gas as opposed to the Innocor where measurements could be completed in 60 seconds.

Measurements of cardiac output, stroke volume, systemic vascular resistance will be done using the Ultrasound Cardiac Output Monitor. We intend to collect data for such as cardiac output, blood pressure, systemic vascular resistance. These will be done with a non-invasive method using the Ultrasonic Cardiac Output Monitor (USCOM). USCOM device is FDA approved for use in adults and pediatric patients and includes a screen and a probe. The Ultrasonic Cardiac Output Monitor was introduced for clinical use in 2001 and measures the velocity of blood flow from either the aortic or pulmonary valve. It has previously been used in studies to measure cardiac output(CCI-09-00102) Cardiac output is the amount of blood pumped by the heart per minute expressed in litres. Cardiac output is a product of heart rate and stroke volume. Blood pressure will be entered manually by which the machine will calculate mean arterial pressure (MAP) and systemic vascular resistance (SVR). SVR =MAP/CO. Knowing changes in cardiac output with the interventions will provide vital information about the critical nature of their illness and this information can be used to tailor therapy for the patients. Our study entails measuring oxygen consumption. One of the fundamental tenets of critical care medicine include matching oxygen delivery to the oxygen consumption. Oxygen consumption that is disparate to the oxygen delivery leads to anaerobic metabolism and may explain the lactic acidosis seen in patients receiving albuterol. Oxygen delivery is the product of arterial oxygen content and cardiac output.

Study participants will be given a questionnaire at the end of each intervention. Oxygen consumption is dependent on many variables such as body temperature, amount of physical activity, amount of caffeine consumed and if they experience any effects such as nausea, palpitations, tremors or jitteriness. Collecting additional information for these confounders will be crucial in analyzing the final outcomes on the two groups with regards to change in oxygen consumption from baseline. The volunteers will also be asked if they have used albuterol or levalbuterol in the past. Albuterol is known to cause various effects such as nausea, palpitations, and tremors or jitteriness and knowledge about theses side effects will help the physicians choose the most appropriate treatment for the subject.

G. Statistical considerations

There is no published information on the increase in oxygen consumption caused by L-Albuterol in humans. Animal studies show oxygen consumption increases from a baseline of 4.8 ± 0.3 ml/kg/min (Newth 1991) to 7.0 ± 0.3 ml/kg/min following L-Albuterol administration. This was an increase in oxygen consumption of 46%. Unpublished pilot data in rhesus monkeys suggests oxygen consumption increases from a baseline of 5.0 ± 0.6 ml/kg/min to 5.26 ± 0.8 ml/kg/min. However, differences in

sedation compared to previous animal studies resulted in greater variability in the measurement of oxygen consumption. We expect racemic albuterol will be associated with a smaller increase in oxygen consumption compared to L-Albuterol. A clinically significant difference in oxygen consumption might be as little as 10% in a child who is critically ill. We will use a paired t-test to compare mean difference in oxygen consumption between L-Albuterol and racemic albuterol in children. Using a paired difference to be detected of 10%, expected standard deviation of 20%, power of 0.9 and significance level (alpha) of 0.05 we calculated a sample size of 44 patients for this study. Given the possibility of drop out or incomplete data collection we anticipate approaching 50 patients to complete the study. Given we cannot be certain that the degree of variability will remain the same across the three cohorts we will target recruitment to 50 subjects in each cohort. We will perform an interim analysis after the first 20 patients are recruited.

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