LONG TERM MEDICATIONS FOR PEDIATRIC ASTHMA:
CONSIDERATIONS FOR TREATMENT

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A thesis submitted in partial fulfillment of
the requirements for the degree of

MASTER OF NURSING

WHITWORTH COLLEGE
WASHINGTON STATE UNIVERSITY
College of Nursing
Intercollegiate Center for Nursing Education

April 1999
To the Faculty of Washington State University:

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Long Term Medications for Pediatric Asthma: Considerations for Treatment

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Abstract

Asthma is a chronic inflammatory disorder of the airways that affects over four million children in the United States, and the incidence of asthma is on the rise. Asthma causes changes in the lung structure, which can lead to more severe disease if not treated. This paper examined the use of the following anti inflammatory medications for the pediatric asthmatic: inhaled mast cell stabilizers, inhaled corticosteroids, and leukotriene receptor antagonists. Studies concluded that there are few known systemic adverse effects of mast cell stabilizer use, but there are some mild local adverse effects. There are adverse systemic effects to be considered with use of inhaled corticosteroids and leukotriene receptor antagonists. The main goal of anti inflammatory use in children is to reduce the incidence of asthma exacerbations. Education issues are also addressed along with issues regarding patient compliance.
Introduction

Asthma is a chronic inflammatory disorder of the airways that affects over four million children and is responsible for more than three million office visits each year (Szilagyi, 1999). The annual cost of treating pediatric asthmatics is greater than 750 million dollars (Szilagyi, 1999). The incidence of asthma is on the rise (NIH, 1997), however, the cause of the increase has yet to be determined. A history of atopy is a strong indicator that asthma will develop, but a single cause is not known (NIH, 1997). Asthma causes changes in the lung structure, which can lead to more severe disease if not treated (Cheang, Gerstner, and Simons, 1997). It is imperative that providers use strategic interventions to reduce the incidence of asthma exacerbations.

The earlier in a patient’s life that the symptoms of asthma occur, the greater the potential for lung remodeling to occur, thus it is imperative that the patient receive proper treatment and education as early as possible. Early intervention, treatment, and education for the pediatric asthmatic and their family can lead to a decrease in symptoms of the disease which may lead to a decrease in lung remodeling causing an increased quality-of-life throughout the patient’s life time (Schneider and Lester, 1997). Respiratory distress and bronchospasm can also cause a decrease in the quality-of-life activities of the pediatric asthmatic patient.

The goal of medical therapy for treating asthma, regardless of the severity, is to prevent symptoms, maintain normal pulmonary function, maintain normal levels of activity, prevent exacerbations, minimize emergency room visits, and provide pharmacotherapy with the least side effects (NIH, 1997). Due to the release of new medications and prescriptive protocol changes over the past two years, treatment plans for the pediatric asthma sufferer are changing.

The three classes of medications that are often used to prevent asthma are mast cell stabilizers, inhaled steroids, and leukotriene antagonists. When used in the treatment of pediatric asthma, mast cell stabilizers and inhaled steroids show a reduction of symptoms and a decrease in hospitalizations (Martinati, Bertoldo, Gasperi, Fortunati, Lo, and Boner, 1998). The effect of Leukotriene antagonists on asthma symptoms is still being studied.

A review of the pathophysiology of asthma serves as a basis for understanding the cause of pediatric asthma and the pharmacological interventions available for the pediatric patient.
Long Term Medications for Pediatric Asthma

Pathophysiology

The mechanism which causes asthma and leads to airway inflammation is a complex interaction between mast cells, eosinophils, macrophages, T lymphocytes, epithelial cells, basophils, and neutrophils (Fisth, 1998). The inflammatory response is often initiated by an allergic "trigger" that starts the inflammatory cascade. Inflammation of the airways causes a reduction in airflow which causes the asthmatic symptoms of wheezing, shortness of breath, and chest tightness (NIH, 1997). Over time if asthma is not treated, collagen is deposited in the lung basement membrane which causes a decrease in lung function and leads to lung remodeling which is irreversible. Asthma is thought to be a genetic IgE cell mediated response (NIH, 1997).

The diameter of a young child's airway is dramatically smaller than an adult's airway. Any inflammation or excess mucous production can lead to a significant decrease in airflow in a short period of time. It is because of this significantly compromised airway that childhood asthma should be treated aggressively. Atopy, or allergic symptoms, is a common indicator of predicting asthma (NIH, 1997). Infants or children who wheeze and have parents who are allergic or asthmatic should be considered for the diagnosis of asthma.

Diagnosis

Asthma can be diagnosed by episodic symptoms of airway obstruction that are reversible when all other differential diagnosis are excluded (NIH, 1997). Peak expiratory flow rates (PEFR) are simple ways to determine airway obstruction, but the definitive test for the diagnosis of asthma is pulmonary function testing which shows obstruction and reversibility (NIH, 1997). The 1997 Guidelines for the Diagnosis and Management of Asthma gives indications for considering a diagnosis of asthma. Some of the indications to be considered when diagnosing asthma are expiratory wheezing, history of cough at night which may awaken the patient, and reversible airflow measurements measured by a peak flow meter (NIH, 1997). After asthma has been diagnosed, it must be classified by symptoms as mild intermittent, mild persistent, moderate persistent, and severe persistent (Table 1) (NIH, 1997).

Children under five years of age require special consideration when making the diagnosis
of asthma. Many of these children will be unable to give an accurate history of symptoms, therefore, the parents must be the historians. A pulmonary function test may not be possible on young patients because of their inability to accurately follow commands. Parents must be asked specific questions regarding the child’s breathing, night symptoms, and seasonal symptoms. Providers must be highly suspicious of asthma for any wheezing child that is seen clinically.

Management

Although asthma is a chronic disease, it can be managed successfully meeting most, if not all, of the therapy goals outlined by the National Institutes of Health (NIH, 1997). Asthma is managed by controlling the symptoms and preventing exacerbations. Prevention of asthmatic bronchospasm is accomplished by the daily use of anti-inflammatory medications for patients with mild persistent asthma to severe asthma. The 1997 National Institute of Health Guidelines for the Diagnosis and Management of Asthma recommend a step approach to therapy with two choices. The choices are to start with high dose inhaled steroid therapy to control the asthma and then step down to the minimal amount of drug necessary to control the asthma, or start with low dose inhaled steroid therapy and gradually increase medications to control symptoms. A controversy exists on deciding when to start infants and young children on steroids. The 1997 guidelines recommend referring infants and children under three years of age who have moderate persistent asthma or require daily medication to a specialist.

Mast Cell Stabilizers

Cromolyn sodium and nedocromil have a proven safety record and have been studied thoroughly and found to be effective in preventing exacerbations of asthma if used as prescribed (Price, Russell, Hindmarsh, Weller, Heaf, and Williams, 1997). Cromolyn and nedocromil work by modulating mast cell mediator release and eosinophil recruitment, which decreases inflammation and inhibits bronchoconstriction (NIH, 1997). These drugs have a long history of use with minimal side effects and a strong safety record. Therefore it is recommended that these drugs be used as a first long-term medication in asthmatic children with mild to moderate asthma (Kumar
and Busse, 1996). The use of cromolyn sodium in children has been shown to be protective against asthma exacerbations (Donahue, Weiss, Livingston, Goetsch, and Greineder, 1997).

Direct comparison of cromolyn and inhaled steroids show that steroids are more effective in severe asthma, but in moderate to severe asthma clear evidence is unavailable as to the superiority of one drug over another (Koning, 1997). A common problem with these drugs is compliance with prescribed dosages. Cromolyn must be taken three to four times daily, and nedocromil must be taken two to four times daily. Compliance is an issue with four time a day dosing, and the effect of these drugs is not immediately felt, which may cause the drug to be discarded by the user because of perceived ineffectiveness.

**Inhaled Corticosteroids**

Inhaled steroids are effective in decreasing the symptoms of asthma and decreasing the inflammatory response that causes bronchoconstriction and scarring of lung tissue (Kumar and Busse, 1996). The use of inhaled steroids has been shown to improve lung function when used over several weeks or months, and may slow the lung remodeling that occurs with asthmatics (Kumar and Busse, 1996). More recent studies show that it is not yet possible to prove whether or not inhaled steroids change or stop lung remodeling (Reijonen and Korppi, 1997). König (1997) states that anti-inflammatory medication should be used with mild asthma, and that the risk to benefit ratio must be determined when choosing medications. Budesonide is a second generation inhaled steroid that has shown marked efficacy in clinical studies and has minimal systemic effects (Kumar and Busse, 1996). Kumar and Busse (1996) state that intervention with budesonide immediately after the initial diagnosis of asthma, can lead to marked improvement in forced expiratory volume in one second (FEV1) when compared to those who started budesonide treatment two years after the diagnosis of asthma has been made (Kumar and Busse, 1996). Budesonide is only one of many inhaled steroids (see table 2) available for use in asthmatics. Other inhaled steroids have been shown to have similar effects (Pauwels, Lofdahl, Postma, Tattersfield, O'Bryne, Barns, and Ullam, 1997). Because of the relatively short period of time it takes for inhaled steroids to work, especially when compared to mast cell stabilizers, some
asthmatics may feel as if they have been cured of asthma because of the effectiveness of steroids. Unfortunately, there is no cure for asthma (Simons, 1997) however, symptoms and exacerbations can be controlled. Providers need to remind and encourage patients to continue using their medication consistently or risk exacerbation of their lung problems.

Adverse systemic effects are a part of every corticosteroid medication use, but inhaled steroids have minimal systemic side effects. However minimal, the fact remains that steroids do have systemic side effects and these effects are just beginning to be recognized. Most distressing to the patient are oral candidiasis, dysphonia, and reflex cough (Kumar and Busse, 1996). Oral candidiasis, dysphonia and the reflex cough can be minimized by rinsing the mouth after each use.

More concerning to providers are the potential systemic effects of adrenal suppression, osteoporosis, and growth retardation in children (Volcheck and O'Connell, 1998). Urinary free cortisol levels were studied with inhaled steroid use, but the information received was inconclusive (Price et al, 1997). Growth is a concern for the pediatric patient taking inhaled steroids, and a study on beclomethasone dipropionate found that children treated with beclomethasone dipropionate were one centimeter shorter that those children treated with a placebo (Kumar and Busse, 1996). More recent studies have shown that growth may be influenced by a multitude of factors, including age, gender, severity of asthma, onset of asthma, and steroid use (Price et al, 1997). Changes in bone density have been found with high doses of inhaled and oral steroids, but it can not yet be determined if bone density is changed by the inhaled corticosteroid or by the asthma itself (Kumar and Busse, 1996). Low dose inhaled steroid use was not associated with a reduction in bone mineral density in a study by Martinati et al (1998). Most studies reviewed showed that inhaled steroids at recommended dosages do not cause significant growth retardation, osteoporosis, or adrenal suppressions.

Recommendations for use of inhaled corticosteroids are controversial. Their use can easily be justified in moderate to severe asthma, but treating mild asthma with inhaled steroids is debatable because of possible adverse effects. Volcheck and O'Connell (1998) recommend starting low dose inhaled steroids for mild persistent asthma (NIH, 1997) or even mild asthma, and Kumar and Busse (1996) recommend the use of high dose inhaled steroids for mild persistent
The idea that early intervention will actually change the pathologic course of asthma makes sense, but has yet to be proven. A follow-up study of children who were hospitalized for asthma and started on anti-inflammatory medication showed that early anti-inflammatory therapy for four months does not decrease in the occurrence of asthma one year later (Reijonen and Korppi, 1998). However, Chaeng, Gerstner, and Simmons (1997) recommend that steroids be used early in the treatment of asthma to improve long term lung function.

**Leukotriene Receptor Antagonists**

Zafirlukast and montelukast are the newest and only FDA approved leukotriene receptor antagonists licensed in the United States. Cysteinyl leukotrienes are potent mediators of inflammation that result in microvascular permeability, mucus secretion, bronchial smooth muscle constriction, and eosinophil proliferation (Lipworth, 1999). The leukotriene antagonist stops this cascade of events which leads to a decrease in bronchial inflammation. With montelukast, peak plasma levels are reached after three hours, and a maximum response can be felt after one day of use (Lipworth, 1999). Because the patient feels the positive effect of the drug after just one day, the patient is usually inclined to consistently take the medication. Another factor in the favor of patient compliance is that montelukast is given once daily and zafirlukast is given twice daily. Zafirlukast has a 40% decrease in bioavailability when taken with food; therefore it should not be taken with food (Lipworth, 1999).

The leukotriene antagonist can be given as monotherapy or in conjunction with inhaled steroids. Leukotriene antagonist therapy usually starts with step two (mild persistent asthma), and has been used for exercised induced asthma (Lipworth, 1999). These drugs may allow for a decrease in steroid dosing for patients on inhaled and oral steroids (Schneider, Mitchell and Lester, 1997). Leukotriene antagonists have been shown to be relatively safe, with the most common adverse effects being headache, diarrhea, and abdominal pain (Lipworth, 1999). Compared with placebo, the occurrence of these adverse effects was similar. Long term studies need to be done, and liver function studies should be done on patients who are at high risk for hepatic injury.
(Lipworth, 1999).

**Education**

Clearly, there are many choices and options for treating pediatric asthma. With all of the choices and options available, it is imperative that the provider consider the compliance of the patient and parents when considering a treatment plan, especially when considering prescribing a mast cell stabilizer. Once the provider has chosen the appropriate therapy for the patient, the key to successful treatment of young patients falls in the hands of the patient and parents. If possible, it is important to include the patient and parents in the treatment decision-making process because compliance may improve if the family feels ownership for the treatment. Some families may realize that it is impossible for them to be compliant with the use of mast cell stabilizers because of the four dose per day requirement. Other families may be so concerned about possible side effects of inhaled steroids that they are willing to adapt to the mast cell stabilizer regimen.

Education plays a significant role in how well the treatment will be carried out. Teaching patients and parents about the medication will improve compliance with the prescribed treatment along with an explanation of why the medication is being used. Due to increased control over medications in the school environment, it is important for providers, parents, and patients to work with the school in developing a medication plan for the child when the rescue medication is needed at school.

**Summary**

Although asthma is a potentially life threatening disease that affects the lives of millions of children, it can be treated successfully. Because of the risk of possible lung damage if left untreated, treating asthma in a preventative manner is beneficial. Today, providers have more pharmacologic options than ever before for the successful preventative treatment of asthma.
Table 1: Classification of Asthma Severity

<table>
<thead>
<tr>
<th>Step</th>
<th>Symptoms</th>
<th>Nighttime Symptoms</th>
<th>Lung Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Mild Intermittent</td>
<td>≤ 2 time a month</td>
<td>FEV1 or PEF ≥80% predicted</td>
</tr>
<tr>
<td></td>
<td>Symptoms ≤ 2 times a week</td>
<td></td>
<td>PEF variability &lt;20%</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic with normal PFT between exacerbations</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exacerbations are brief (a few hours to a few days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2</td>
<td>Mild Persistent</td>
<td>&gt;2 times a month</td>
<td>FEV1 or PEF ≥ 80% predicted</td>
</tr>
<tr>
<td></td>
<td>Symptoms ≥ 2 times a week but &lt; 1 time per day</td>
<td></td>
<td>PEF variability 20-30%</td>
</tr>
<tr>
<td></td>
<td>Exacerbations may affect activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 3</td>
<td>Moderate Persistent</td>
<td>&gt;1 time a week</td>
<td>FEV1 or PEF &gt;60%&lt;80% predicted</td>
</tr>
<tr>
<td></td>
<td>Daily Symptoms</td>
<td></td>
<td>PEF variability &gt;30%</td>
</tr>
<tr>
<td></td>
<td>Daily use of beta2 agonist</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exacerbations affect activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exacerbations ≥ 2 times a week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 4</td>
<td>Severe Persistent</td>
<td>Frequent</td>
<td>FEV1 or PEF≤60% predicted</td>
</tr>
<tr>
<td></td>
<td>Continual Symptoms</td>
<td></td>
<td>PEF variability &gt;30%</td>
</tr>
<tr>
<td></td>
<td>Limited Physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequent exacerbations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FEV = force expiratory volume in 1 second; PEF = peak expiratory flow
Adapted from the National Asthma Education Program Expert Panel (NIH, 1997).
<table>
<thead>
<tr>
<th>Non-Steroidal Anti-inflammatory</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cromolyn MDI Nebulized solution</td>
<td>2 puff 3-4 times daily 2ml 3-4 times daily</td>
<td>Local irritation, bronchospasm</td>
</tr>
<tr>
<td>Nedocromil</td>
<td>2 puffs 4 times daily</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Leukotriene Antagonist</th>
<th>Dose</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast</td>
<td>Children &gt; 6-14 years Children 5mg po daily Adults 10mg po daily</td>
<td></td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>Children &gt; 12 years old 20mg bid</td>
<td>Should be taken 1 hour before or 2 hours after meals</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inhaled Steroids</th>
<th>Dose</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone Dipropionate Beclomethasone DS (Vanceril, Beclovent)</td>
<td>2-4 puffs 4 times daily</td>
<td>Oral rinse should be done after each use to minimize local effects of dysphonia and thrush</td>
</tr>
<tr>
<td>Triamcinolone Acetonide (Azmacort) Flunisolide (Aerobid)</td>
<td>2-4 puffs 4 times daily 2-4 puffs 4 times daily</td>
<td></td>
</tr>
<tr>
<td>Fluticasone (Flovent)</td>
<td>2-4 puffs 2 times daily (available in 44, 110, 220 mcg/puff)</td>
<td></td>
</tr>
<tr>
<td>Fluticasone DPI (Rotadisk)</td>
<td>2-4 puffs 2 times daily (available in 40, 100, 250mcg/puff)</td>
<td></td>
</tr>
<tr>
<td>Budesonide (Pulmicort Turbuhaler)</td>
<td>2 puffs 2 times per day</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from St. Mary’s Children Hospital (1998)
References


Mary Bridge Children’s Hospital (1998). Pediatric respiratory therapy medication dosages
guidelines. (Brochure)


Eric Dudenhofer

702 clinical research participation

Research Participation and Utilization

Name and Type of Research Project: A Stratified, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group 12-Week Trial Evaluating the Safety And Efficacy of Alternative Delivery Systems For Inhaled Asthma Medications. The study was being conducted at Spokane Allergy and Asthma Clinic.

Goals and Purpose of Study: The goals of the study are to test the safety and efficacy of medications that are given by metered dose inhalers that do not contain CFCs. The drugs being studied are salmeterol and fluticasone propionate. A combination of salmeterol/fluticasone will be compared to the effectiveness of each individual drug compared against placebo. All drugs will be administered through rotodisk inhalers.

Student's Role in Study: The student operated as a data collector, in that he assisted with the collection and recording of data for the study. He also participated in patient teaching about the use of the medications.

Results of the Study: The study being done was in the initial stages and no data had yet been released. Patients were still being signed up for the project. Results should be available in about six months.

What the Student Learned While Participating in the Research: He learned that clinical research is complex and all records must be done in exactly the correct way, or they must be redone. The FDA takes an active role in making sure that all aspects of the study are done correctly. The studies are usually thought out in detail and the exact protocol must be followed to
verify the results. Research is also interesting and challenging in that new treatments are being attempted to solve real problems. This student plans to use research in his practice by looking for patients who may benefit from using investigational drugs. He also plans to review the research protocol that was developed for each new drug that he is presented with to ensure that the claims being made match the results of the study.