Original Article

Oral versus inhaled bronchodilators in pediatric practice at a rural health care setting

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Abstract: Background: *The majority of pediatric asthma cases are managed entirely within general practice; selecting the appropriate type of therapy for the wheezy infant with no previous asthma history often becomes a dilemma for clinicians.* Aim: *To compare the improvement in asthma exacerbations, after administration of oral or inhaled bronchodilator therapy, in children with newly diagnosed mild to moderate asthma.* Material and methods: *A total of 128 children aged 6 months to 14 years with asthma symptoms were referred at a rural health care setting. Detailed case history was obtained and peak flow monitoring was performed when feasible. Group A, 58 children aged 2.94±2.57 years, received oral and Group B, 70 children aged 8.26±4.43 years, inhaled therapy. All children were re-examined 3 days and 7 days from onset of treatment.* Results: *Improvement was noticed in 43/58 (74.1%) and 67/70 (95.7%) patients of groups A and B respectively ($p \leq 0.001$) 3 and 7 days after the onset of treatment. Treatment was changed in 10 and 8 patients of each group respectively ($p > 0.05$). Compliance was better in Group A ($p \leq 0.001$). Fifty-two patients of Group B and no patients of Group A required further training ($p \leq 0.001$). Inhaled bronchodilator therapy has led to a significant remission of asthma exacerbations compared to oral bronchodilator therapy.* Conclusions: *Although there has been better compliance and no need for additional education in the patients receiving the oral therapy, the latter should be reserved only for children usually less than 2-3 years of age with mild occasional asthma, or for older children who seem not to be competent using the inhaled therapy on their first visit. Parents should be encouraged and trained to use inhaled rather than oral regimens in all age groups of children. Hippokratia 2006; 10(2): 80-84*

Key words: *asthma, oral therapy, inhaled bronchodilators, peak expiratory flow rate*

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Introduction

Pediatric asthma is the leading chronic inflammatory disorder of the airways in childhood characterized by hyperreactivity that either resolves or at least improves with age and an unusually complex management challenge because of the anxiety caused in the parents and the inconsistency of response to therapy. The diagnosis of asthma for the majority of children is mainly clinical, and is based on a history of recurrent or persistent wheeze in the absence of any other apparent cause (Table 1). The first episode of wheezing may be difficult to distinguish from acute bronchiolitis in infants or viral bronchitis in children.

The majority of patients are managed entirely in a primary care setting[1]. Very few require hospital referral or admission in the hospital. Inhalation of bronchodilators and corticosteroids is the mainstay of treatment for patients with asthma[2]. The clinician often faces a dilemma selecting the appropriate type of therapy for the wheezy infant presenting with no previous history of asthma. The present study was conducted in children of a Greek rural area with newly diagnosed mild to moderate asthma: a) to compare the improvement in asthma exacerbations, after administration of oral or inhaled bronchodilator therapy, and b) to assess the type of bronchodilator regimen (administered according to the patients' age) with the compliance, and the need for education of patients and/or their parents.

Material and Methods

This prospective, non-randomized study was carried out at the pediatric department of our rural Health Center (Gonni, Larissa, Greece). One hundred and twenty eight patients (77 male, 51 female) aged 6 months to 14 years (mean age: 6.3±4.1 years) were referred to our pediatric department for asthma. The diagnosis of asthma was based mainly on its symptoms such as recurrent non-specific dry cough often accompanied by wheeze and episodes of shortness of breath, delayed expiration, and abdominal pain. The coughing paroxysm exacerbated in the early hours of the morning and during exercise, and was sometimes followed by a vomit. To ensure that all patients were evaluated with uniform criteria, the same qualified pediatrician assessed the symptoms relevant to asthma in all the patients. Moreover, assessment of the peak expiratory flow rate (PEFR), performed in competent children usually over 6 years old, was based on the guidelines for asthma diagnosis and management, published by the National Asthma Education and Prevention Program[3]. From the present study were

excluded children with previously diagnosed asthma who had received bronchodilator therapy in the past, taking any drugs (bronchodilators) prior to enrolment in the study, requiring corticosteroids or other asthma medications, suffering from bronchiolitis, pneumonia and/or seasonal viral infection, with severe or life-threatening asthma, as well as the patients experiencing wheeze associated with fever and cough. Patients with symptoms suggesting gastroesophageal reflux disease were also excluded.

Detailed history was obtained for each of the patients with following parameters: age, sex, number of episodes, presence of dyspnea, compliance, and education prospects in parents and/or patients. A chest radiograph was taken to exclude diseases other than asthma that presented with recurrent cough or wheeze.

Table 1. Differential diagnosis of asthma.

Transient infant wheezing
Aspiration (usually from milk)-cough during feeds
Gastroesophageal reflux disease
Bronchopulmonary dysplasia
Sinusitis
Vocal cord dysfunction (often mimics asthma)
Cystic fibrosis
Inhaled foreign body
Structural abnormalities (i.e., vascular ring, mediastinal mass)
Cardiac abnormalities associated with congestive heart failure
Tuberculosis
Bronchiolitis
Pertussis

The patients were divided into 2 groups according to the therapy they received. In our study we decided not to randomize our patients, but to encourage the use of inhaled therapy in all co-operative patients and their parents. We deemed that blind randomization of our patients to the two types of regimen would be inapplicable or unethical and a malpractice, because such an event would be against the evidence-based medicine, as expressed by the guidelines for asthma diagnosis and management[3]. Therefore, the patients assigned to oral therapy were the younger ones (usually less than 2-3 years of age), who were not expected to exhibit perception over the use of the inhaling device or older children who demonstrated diminished perception over the use of the above-mentioned device during their first visit. All the other patients were assigned to receive inhaled therapy. Group A consisted of 58 patients aged 2.94±2.57 years that received oral therapy [syrup salbutamol (2 mg/5 mL) 0.15 mg/kg/dose every 6 hours; maximum single oral dose of 4 mg]. Group B consisted of 70 patients aged 8.26±4.43 years that were administered inhaled bronchodilators [salbutamol 100 mcg/inhalation 1-2 inhalations as required 3-6 hourly (for acute symptoms, 4 - 6 inhalations if <6 years; 8-12 inhalations if >6 years)], or nebulizer solutions [salbutamol (5 mg/mL) 0.02 mL/kg/dose to a maximum of 1mL diluted with saline every 3-6 hours] at the Health Center (followed by inhaled bronchodilators at home). Fifteen patients of group A and 23 patients of group B additionally received high concentrations of oxygen (≥60%).

Peak flow monitoring was performed between 9:00 a.m. and 14:00 p.m. in cooperative and competent children of Group B usually older than 6 years of age with moderate-to-severe persistent exacerbations of asthma, prior to and 15 to 20 minutes after the initiation of inhaled bronchodilator therapy, in order to: a) determine severity of the exacerbation; b) evaluate the patient's response to bronchodilator therapy by reversibility tests; and c) guide therapeutic decisions at home[3]. In each case, the best of three trials of peak expiratory flow rate (PEFR) was obtained, using the Wright peak flow meter. In Group A patients routine peak flow monitoring was not performed as it has been shown to be inconsistent in infants and several preschool children.

All the patients were re-examined after 3 days and 7 days from onset of treatment by the same qualified pediatrician, and evaluation of the efficacy of each regimen was assessed. As improvement in asthma exacerbations was defined remission of recurrent non-specific dry cough, wheezing, episodes of shortness of breath, delayed expiration, and abdominal pain. Moreover, an increase in PEFR values ≥20%, 15 to 20 minutes after the inhaled therapy, was also considered as improvement. On their subsequent visits (days 3 and 7 from onset of treatment), compliance was evaluated by asking the patients and/or the parents to demonstrate or explain the way they received the medication; they were also requested to report any adverse effects that they may have experienced. Modification of therapy was necessary in a number of patients in each group during their second visit. After the initial guidelines provided on their first visit, patients and/or parents were later offered the opportunity of additional education over the correct use of inhaled bronchodilators through a special school of asthma. All parents gave informed consent of the therapy provided to their children. The study was not reviewed by an institutional review board, because there is not one available in our prefecture. Instead, the study was discussed with 2 individual pediatricians who were not involved in the study, and was conducted in accordance with the "Guidelines for the Diagnosis and Management of Asthma", issued by the NIH Expert Panel (U.S. Department of Health and Human Services)[3].

For the patients' age (years) the Mann-Whitney U test was used, whereas for gender the chi square test was applied. The latter test was also used to assess the efficacy of the various bronchodilator therapies, the compliance of the patients and/or the parents, and the necessity for well established individual education regarding the correct use of the medication. Significance was set at $p<0.05$.

Results

Table 2 summarizes the demographic data and the

outcome of the applied regimen in each group. Gender did not differ statistically in both groups. Presence of dyspnea was noticed in 27 out of 58 (46.6%) patients of Group A and in 41 out of 70 (58.6%) patients of Group B (P>0.05). Recurrent non-specific dry cough was present in all patients. Other less frequent symptoms included non-specific lower abdominal pain without concomitant upper gastrointestinal symptoms (n=5) and mild fever (n=3). There were no cases with life threatening symptoms that would require immediate hospitalization of the patient.

Table 2. Efficacy of the bronchodilator regimens in the 2 study groups.

Parameter	Group A (n=58)	Group B (n=70)	Odds Ratio (95% CI**)	Significance p (A vs. B)
Age (mean±SD*, years)	2.94±2.57	8.26±4.43	...	<0.001
Sex (male:female)	37:21	40:30	...	NS***
Dyspnea	27 (46.6%)	41 (58.6%)	0.72 (0.36-1.46)	NS
Improvement in symptoms (3 and 7 days from onset of treatment)	43 (74.1%)	67 (95.7%)	0.13 (0.03-0.51)	≤0.001
Modification in regimen during 2nd visit	10 (17.2%)	8 (11.4%)	1.61 (0.58-4.48)	NS
Compliance of patients and/or guardians	49 (84.5%)	29 (41.4%)	7.72 (3.36-17.73)	≤0.001
Individual education needed	0 (0%)	52 (74.3%)	0	≤0.001

*SD: standard deviation; **CI: confidence interval; ***NS: non-significant; ellipses indicate not applicable

Twenty three out of 70 (32.9%) patients of Group B usually over 6 years of age underwent peak flow monitoring that revealed a PEFR >60% of predicted or personal best, prior to the administration of bronchodilator therapy. All PEFR values improved ≥20% 15 to 20 minutes after the inhaled therapy.

During the second visit at the Health Center, asthma symptoms were relieved in 43 (74.1%) and in 67 (95.7%) patients of groups A and B respectively (odds ratio: 0.13, 95% Confidence Interval 0.03-0.51; p≤0.001). This improvement was maintained 7 days after onset of treatment. The treatment was altered in 10 (17.2%) and in 8 (11.4%) patients of groups A and B respectively (p>0.05) during the second visit. Compliance differed statistically between the two groups in favor of Group A (p≤0.001). Individual education was not needed in any of the patients of Group A, whereas 52 (74.3%) patients of Group B required further training (p≤0.001).

Administration of salbutamol was well tolerated in both groups. Adverse effects were generally minor and included few cases of headache and nausea. There was only one case of a one-year-old male infant who exhibited tremor after the administration of inhaled therapy and discontinuation of treatment led to remission of tremor.

Discussion

Asthma is a quite frequent problem in children with increasing incidence despite excellent treatments available. An estimated 70 per 100,000 for the preschool age group and 50 per 100,000 for older children new cases of pediatric asthma have been reported[4]. Fifty to 80 percent of children with asthma develop symptoms before five years of age[5]. Factors associated with the onset of symptoms include allergy, family history of asthma or allergy, perinatal exposure to tobacco smoke, viral respiratory infections, gastroesophageal reflux disease[6]. Predisposing factors are male gender and low birth weight[7]. In our study, male gender accounted for 60% of the total number of patients that were included. Factors triggering pediatric asthma triggers include allergens, pharmacologic agents, physical factors and physiologic conditions (e.g., stress, respiratory infection and rhinitis)[8]. Interestingly, specific factors have been acknowledged that reduce the risk for persistent disease. In these cases, increased contact with other children, pets or farm animals in early life may decrease the severity or protect against the progress of asthma in children[9]. In rural areas, children are often exposed to these factors and this might be the reason why asthma has not dramatically deteriorated in any of our patients, since the area covered by our Health Center is mainly agricultural, with each separate village having a population of less than 4,000-5,000 inhabitants.

In most children with asthma, the primary diagnostic tool is clinical assessment, a parameter that was mainly applied in our study. Obtaining a medical history could identify symptom patterns, severity of symptoms and precipitating factors, and could also support the diagnosis of asthma. Wheezing during the first year of life is often a transient condition, which improves with time. It appears to be related to early life reduced small airway calibre. Wheezing that begins or persists into the second year of life is usually associated with a different abnormality of the airways. Onset or persistence of wheezing in the second year of life may be part of the clinical entity recognized as asthma[10]. Since treatment options do not vary much in infants less than one year of age compared to older children[11], we considered these infants eligible for our study protocol, despite the fact that definite diagnosis of asthma could not be reached.

In our clinical practice, chest radiography facilitated the diagnosis of asthma for the elimination of other illnesses that may present with recurrent cough or wheeze (Table 1)[12].

Due to the fact that pulmonary function tests should also be conducted to confirm the diagnosis[13], we used flow meters that are portable, affordable, and less time consuming. Although routine pulmonary function screening is inconsistent in infants and several preschool children, these tests may be a more reliable indicator in cooperative and competent children who are usually over 6 years of age, even though considerable variation still exists because of poor effort-dependent technique, the use of sizeable equipment[14], patient and possibly his/her parents education status, medications, and variability among different populations[3,15]. As shown in figure 1, we considered a standard algorithm for the diagnosis of asthma, based on PEFR measurements. PEFR and its variability were also employed to assess asthma severity. In mild intermittent and mild persistent types of asthma PEFR is for both ≥80% than that predicted, and its variability is <20% and between 20 and 30%, respectively. On the other hand, in moderate persistent or severe persistent types of asthma PEFR is >60% to <80%, and ≤60% than that predicted, respectively, whereas PEFR variability is found >30% for both types[3]. According to the above-mentioned data, in our study there were no patients with severe persistent asthma included.

Short-acting beta-2 agonists are the therapy of choice to relieve acute symptoms of bronchospasm, a regimen that has been applied in our study. Indeed, these agents have a good safety record and are available in both oral and inhaler forms. Inhaler form is preferred because it is more effective and has less adverse effects. The dose of the drug is much less in inhaled than in oral adrenergic bronchodilator drugs, because only a small fraction of salbutamol syrup reaches the lungs and benefits the patient, while a major amount of syrup is distributed in other organs. Instead, inhalers produce quick relief since the drug is directly deposited in the lung. The most preferred inhaling type of medication is inhaler, since a spacer with an attached face-mask can be applied, which is particularly useful for children up to 4-5 years. If inhaler is received through a spacer 20% dose is distributed in the lungs and 80% is retained in the spacer, thereby resulting in drastic further decrease of the dose of drug retained in the body. Nevertheless, oral bronchodilators are used because they are cheaper and require practically no education to use. However, they should be discouraged because oral administration slows the onset of action (30-60 minutes) and increases the incidence of behavioral side effects and sleep disturbance. In our study we were obliged not to randomize our patients, but to encourage the use of inhaled therapy in all co-operative patients. Although this might be considered as a limitation in our study, we deemed that blind randomisation of our patients to the two types of regimen would have been inapplicable or unethical and a malpractice, because such a thing would be against the evidence-based medicine. Moreover, it has been shown that the relationships between diverse variables (biological or psychosocial) in the first year and school-age asthma are common, and they support the formulation of asthma

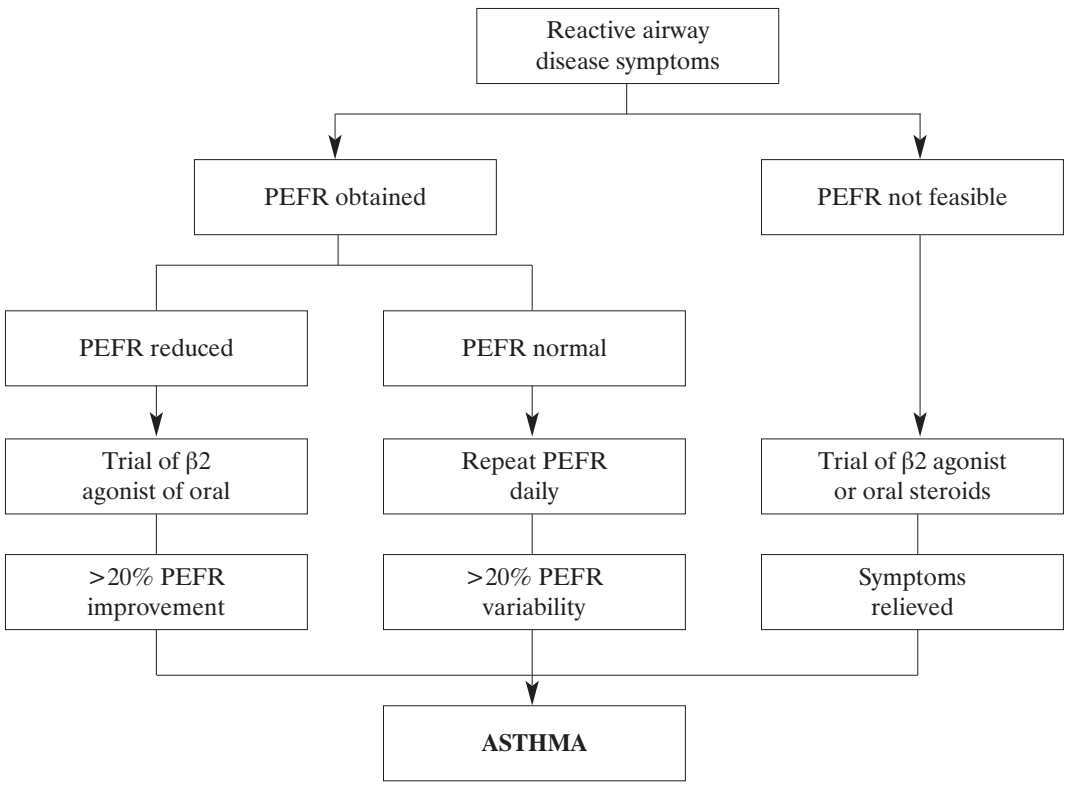

Figure 1. Algorithm for the diagnosis of asthma (PEFR: peak expiratory flow rate).

as beginning early in life[16]. Therefore, the course of asthma and its therapeutic approach are the same for both the younger and the older children, allowing us for comparisons in response to basically the same treatment (salbutamol). In this regard, our patients who received the oral therapy were the younger ones or older children who demonstrated diminished perception over the use of the inhaling device during their first visit.

The review of our patients took place after only 3 and 7 days, because if the symptoms persisted after these days, we would change the regimen or refer our patients to the nearest hospital. In addition, despite our efforts, a possibility of a self-limiting illness cannot be entirely excluded; however, this is a universal bias for both groups of patients, thereby not affecting significantly the final outcome. In our study the treatment was altered if asthma symptoms improved or relapsed[17]. In case of deterioration, we administered long-term-control medications [i.e., anti-inflammatory agents (sodium cromoglycate or inhaled corticosteroids), long-acting bronchodilators, or leukotriene modifiers]. Importantly, we provided the patients (who were on oral therapy) or their parents with better training for the use of the inhaling devices. In this regard, we noticed that poor compliance was a major problem in pediatric asthma management. Factors contributing to poor compliance include: route of administration (oral therapy is preferred to inhaled)[18], complexity of regimen[19], medication effects (a slow onset of action and long duration on discontinuance have poor adherence rates), concern of adverse effects[8], cost-effectiveness of treatment (the use of a spacer in the inhaled regimen increases the cost considerably), and the fact that regular medication constantly reminds the parents that they have an ill child[20]. Hence, there was poor control of the underlying inflammation and bronchoconstriction, which might contribute to future development of severe exacerbations and possibly to irreversible damage to the lungs (airway remodeling)[21].

Considering all above-mentioned data existing in a rural area, we conclude that individual education of each patient and/or parent through a school of asthma is fundamental for effective acute-phase management of this disease. This important task has been undertaken by a trained nurse under the guidance of the pediatrician. Through this school it has become clear that the patients and/or their guardians need to understand asthma, but they should not be overwhelmed with too much information at once. Practices should focus to inhaler technique and to the use of peak flow meter. Education also includes understanding treatment, how to change therapy, when to contact the doctor, how to manage or avoid trigger factors, and obtaining general knowledge of asthma[22]. Oral therapy should be reserved only for children usually less than 2-3 years of age with mild occasional asthma, after it is made obvious that the inhaled therapy will not be received according to the doctor's instructions. Cooperation between family doctors, hospital and patient and/or its guardian is essential for successful asthma care.

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