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Is Oral Dexamethasone Safe and Effective for Treating Asthma Exacerbations In Pediatric Patients?

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A Selective Evidence Based Medicine Review

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Abstract

OBJECTIVE: The objective of this selective evidence based medicine review is to determine whether or not a one or two dose regimen of dexamethasone (DEX) is a safe and effective treatment for asthma exacerbations in the pediatric population.

STUDY DESIGN: Review of three English language, primary randomized controlled trials (RCT) published from 2001-2008.

DATA SOURCES: Three RCTs examining the efficacy of DEX either in a single dose or one dose for two days, compared to a traditional five day regimen of prednisone (PRED).

OUTCOMES MEASURED: The studies examined the number of relapses within 10 days of using DEX or PRED, the number of subjects with unscheduled returns to the emergency department (ED) or other health care facility within 5 days, and episodes of emesis after administration of drug in the ED and at home within 5 days.

RESULTS: These studies concluded that both a single dose and two doses of DEX was no less effective than a five day regimen of PRED, specifically in regards to relapse rates and time to recovery. DEX did not lead to a higher rate of emesis than PRED either in the ED or within five days of initial treatment.

CONCLUSIONS: DEX is equally effective to PRED in the treatment of acute asthma exacerbations in pediatric patients, and does not lead to a greater rate of emesis within 5 days of treatment. Because DEX can be administered in a single dose or in a two day regimen, instead of the five day regimen required of PRED, patients may be more satisfied and have a higher compliance rate by using DEX.

KEY WORDS: Asthma, dexamethasone, pediatric

Introduction

Asthma is a chronic airway disease characterized by inflammation, airway hyper-reactivity, and reversible airway obstruction. It is likely that both an environmental and genetic component contribute to the etiology of the disease. Extrinsic factors contributing to asthma include atopic factors, environmental triggers, exercise, and early childhood infections. The airway of an asthmatic patient may include hyperplasia of the mucus glands, altered architecture of the airways that results from chronic inflammation and scarring, and bronchoconstriction. Common symptoms include wheezing, coughing, and shortness of breath.

Approximately 25 million individuals in America have asthma, 7.1 million of which are children under 18 years of age [1, 2]. Over nine percent of children in America suffer from asthma, and it is considered to be the most common chronic disease of childhood [1]. Since 1980, the prevalence has been steadily increasing [1]. Asthma is an extremely common disease that many physician assistants (PA) are likely to encounter on a regular basis. Both the management of asthma and the treatment of its exacerbations are within the scope of the PA practice.

The cost of managing asthma is similarly prodigious. The estimated cumulative cost of asthma, per year, is $56 billion [5]. The average annual cost for an individual to manage their asthma was found to be $3300 in medical expenses [5]. The average cost of an ED visit for asthma exacerbation is $210, or up to $3102 if the patient is admitted [3].

Asthma exacerbations account for approximately 1.75 million visits to the ED a year [3]. It is estimated that 2.57 million individuals had asthma in 2010, and the prevalence of asthma is currently at its highest, with an increased prevalence in pediatric patients [6]. The number of ED visits per 100 individuals with asthma has not declined in the past ten years [6].

Many variants of asthma have been documented, including atopic and non-atopic types, exercise induced, occupational, and cough variant asthma. The onset of asthma is often in childhood, although adult-onset variants also exist. Atopy is the greatest risk factor for asthma, but other risk factors include obesity, urban city dwelling, and asthma in either or both parents [7].

Pulmonary function testing is used to formally diagnose asthma. An expert panel has created a classification of asthma and a stepwise treatment approach [8]. Treatment begins with patient education, such as recognizing exacerbations, and lifestyle modifications, including avoiding environmental triggers. Medical management can be divided into short and long term control modalities. Short-term control begins with a short acting beta agonist inhaler. Ipratropium bromide is a possible adjunct. Long-term control begins with long acting beta agonist inhalers and inhaled corticosteroids; leukotriene agonists and mast cell stabilizers are adjuncts more commonly used in atopic asthma. Exacerbations are typically managed with oral or intravenous corticosteroids. Magnesium, oxygen, heliox, and airway management including intubation may be used in severe cases [7].

Objective

The objective of this selective EBM review is to determine whether or not a one or two dose regimen of dexamethasone is a safe and effective treatment for asthma exacerbations in the pediatric population

Methods

The population studied were children aged 2-18 presenting to the ED with a mild to

moderate asthma exacerbation with a history of asthma-like symptoms relieved with a beta-antagonist.

The intervention in two of the studies was oral DEX once a day for two days. The third study (Altamimi) used a single dose of oral DEX. All of the studies used a five-day regimen of PRED as a control, although the exact dosing of these varied to a slight degree. Both the Greenberg and Altima studies used oral PRED twice daily for 5 days; the Qureshi study used oral PRED in the ED, followed by once daily PRED for 4 days.

The outcomes measured include unscheduled returns to the ED or relapse within 10 days, emesis with administration of drug, or within 5 days at home, return to baseline, days missed of school or work, length of stay, and hospital admission. The studies include three prospective, randomized trials, two of which were double-blinded and one (Qureshi) that was not.

The author found these three RCTs, all published in English in peer-reviewed journals between 2001 and 2008, using PubMed and OVID. The keywords used included asthma, dexamethasone, and pediatric. This author conducted the research, and selected the articles based on specific inclusion and exclusion data and comparability of data. Inclusion criteria included the focus of the article being patient oriented evidence that matters (POEM), and the articles being RCTs published after 2000. Exclusion criteria included any type of study which was not a RCT, or studies which involved a population younger than 2 or older than 18. The statistics reported in this review include the p-value, odds ratio (OR), confidence interval (CI), numbers needed to treat (NNT), numbers needed to harm (NNH) absolute risk reduction (ARR), relative risk reduction (RRR), relative benefit increase (RBI), and absolute benefit increase (ABI). Table 1 includes the demographics of the included studies.

Outcomes Measured

These studies measured the number of subjects with unscheduled returns to the ED or other medical facility, due to symptoms of asthma, within 5 or 10 days. The frequency of emesis was also measured; patients reported emesis via a patient self assessment score sheet, which was later reviewed with them by an investigator, or reported directly to an investigator on scheduled follow up, or emesis was observed in the ED with administration of the DEX or PRED. Other outcomes measured include return to baseline, missed days of school or work, length of stay in the ED, and admissions to the hospital.

Results

This review examined three RCTs including children aged 2-18 with a known history of asthma, and compared the intervention of a one or two day course of DEX compared to the traditional five day regimen of PRED. All studies included adolescent patients presenting to the ED with an exacerbation of asthma.

The Altamimi study population included 110 children, and was conducted as a double blind RCT. The patients were randomized into two groups, one receiving a single dose of oral DEX (0.6 mg/kg to a maximum of 18 mg) and the other a five day regimen of oral PRED twice daily (1 mg/kg per dose to a maximum of 30 mg). The inclusion criteria included children aged 2 to 16 presenting to the ED with exacerbations of mild to moderate asthma. All participants had a history of at least 1 prior episode suggesting asthma, which was treated with albuterol. Patients with severe asthma on presentation (peak expiratory flow reading (PEFR) less than 60%), complete recovery after salbutamol treatment, use of oral steroids in past 2 weeks, history of severe asthma exacerbation, prior intubation or admission to an intensive care unit (ICU), or

Table 1: Demographics of included studies

Study and Type	# Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Altamimi (2006) [13] Double blind RCT	134	2-16	Children 2-16 y/o presenting to ED with exacerbation of mild to moderate asthma At least 1 prior episode suggesting asthma, treated with albuterol	- Signs of severe asthma on presentation (PEFR less than 60%, PIS of 10 or more), complete recovery after the first salbutamol therapy, use of oral steroids over the last 2 weeks, hx of severe asthma exacerbation, prior intubation or intensive care unit (ICU) admission for asthma, chronic lung disease, heart disease, neurological disorder, psychiatric disease, history of acute allergic reaction, active chickenpox, or herpes simplex infections	24	Single dose oral dexamethasone (0.6 mg/kg to a maximum of 18 mg)
Greenberg (2008) [14] Double blind RCT	108	2-18	Children aged 2 to 18 presenting to the ED with an acute asthma exacerbation All patients had two or more episodes of wheezing treated with a beta-adrenergic agonist drug	Use of oral steroids in the past month, hx of intubation for a previous asthma exacerbation, Varicella exposure in the past 3 weeks, Possible FB aspiration, Any chronic lung disease, Chronic heart, liver, or kidney disease, significant respiratory distress necessitating airway intervention, Previous enrollment in this study, no telephone for follow-up, two or more episodes of emesis after steroid given in ED	18	Oral dexamethasone (0.6 mg/kg to a maximum of 16 mg) once a day for 2 days
Qureshi (2001) [15] RCT	628	2-18	Pts aged 2-18 years with a past hx of asthma defined as 2 or more episodes of wheezing where beta-adrenergic agonists were used for treatment, required 2 or more albuterol tx in ED	Use of oral corticosteroids 4 weeks prior to the current exacerbation, Hx of intubation, Varicella exposure in prior 3 weeks, Concurrent stridor, Possibility of an intrathoracic FB, Chronic respiratory disease, Cardiac disease, Immediate airway intervention required	95	Oral dexamethasone (0.6 mg/kg to a maximum of 18 mg) qd for 2d

chronic lung disease, neurological, psychiatric or heart disease, history of acute allergic reaction, herpes infection or active varicella infection, were excluded. Regarding compliance, only one patient in the PRED group and five in the DEX group received less than 80% of prescribed medicine. This was measured by counting the remaining medicine in the dispensed pill bottle; of note, those non-compliant in the DEX group missed only placebo doses as they received DEX in the ED.

Those in the DEX group had a shorter length of stay in the ED (3.5 $\pm$ 1.93) compared to those taking PRED (4.3 $\pm$ 3.67 hours) (CI -1.8, 0.2). Each group required an average of 3.9 salbutamol treatments (CI -0.51, 0.51), and the severity of asthma upon discharge was the same (CI -0.36, 0.56), as was the number of admissions (9% vs 13.4% respectively). Four subjects in the DEX group compared to one subject in the PRED group returned to the ED with persistent symptoms. A peak self-assessment score (PSAS) was used to quantify symptoms. The amount of days for PSAS to return to baseline was 5.21 for the DEX group and 5.22 for the PRED group (CI -0.7, 0.68). Two subjects in the PRED group withdrew from the study due to repeated emesis. On day five of follow up, one subject from the PRED and none from the DEX group reported emesis, and the NNH was -100, so that it would take 100 patients receiving DEX to have one fewer episode of emesis (RRR=2.664, ARR=0.0477). The primary outcome showed that DEX was slightly more effective in preventing relapses, and the NNT was 21, so that for every 21 patients given DEX, one more would have relapse prevention over PRED (RRI=-1, ARI=-0.01). Data from the intent to treat analysis is presented in Table 2.

The Greenberg study population included 89 children, and was conducted as a double blind RCT. The patients were randomized into two groups, one receiving oral DEX (0.6 mg/kg to a maximum of 16 mg) once a day for two days, and the other a five day regimen of oral PRED

twice daily (1 mg/kg per dose to a maximum of 30 mg). The inclusion criteria included children aged 2 to 18 presenting to the ED with an acute asthma exacerbation, and a history of two or more episodes of wheezing treated with a beta-adrenergic agonist drug. Patients with oral steroid use in the past month, history of intubation, varicella exposure in prior 3 weeks, possible foreign body aspiration, chronic heart, liver, kidney or lung disease, symptoms necessitating intubation, prior enrollment in this study, no telephone for follow up, or two or more episodes of emesis in the ED after steroid administration, were excluded from the study. No patients necessitated exclusion due to non-compliance.

Patients from both the DEX and PRED group did not differ in the quantity of breathing treatments in the prior 24 hours preceding presentation to ED. Presenting vital signs, including temperature, heart rate, respiratory rate, systolic blood pressure and pulse oximetry, did not differ between the two groups. A pediatric asthma score (PAS), used to gauge severity of asthma, was higher on presentation in the DEX group (P 0.003). The primary outcome studied was need for unscheduled follow up. There was no significant difference found in this outcome: 8 patients in the DEX group (16%) and 3 in the PRED group (8%) required unscheduled follow-up (P 0.27). The analysis showed DEX to be as or more effective than PRED in preventing relapse (RRR= 0.50, ARR=0.08, NNT=13). Five patients in the DEX group (10%) and 7 in the PRED group (18%) had emesis in the ED (P 0.24). DEX may infer an advantage in preventing adverse effects (RRI=0.44, ARI=-0.08, NNH=-12). Data from the intent to treat analysis is in Table 3.

The Qureshi trial was a RCT, which was not double blinded because DEX tablets were used versus PRED suspension or tablets. Because the decision to return for treatment after being discharged from the ED was solely based on the parents' discretion, potential investigator bias was minimized. This study included children aged 2 to 18 presenting to the ED with an acute

asthma exacerbation, and with a history of asthma, defined by two or more episodes of wheezing treated with beta-adrenergic agonists; also the children included required 2 or more albuterol nebulizer treatments in the ED. Children with use of oral steroids in the prior month, varicella exposure in prior 3 weeks, history of intubation or need for immediate airway intervention, concurrent stridor, possibility of inhaled foreign body, or chronic respiratory or cardiac disease, were excluded from the trial.

The patients were randomized into two groups, one receiving oral DEX (0.6 mg/kg to a maximum of 18 mg) once a day for two days, and the other receiving oral PRED (2 mg/kg per dose to a maximum of 60 mg) in the ED, followed by a once daily dose of PRED (1 mg/kg/dose) for four more days. Of note, compliance did differ between the two groups. In the PRED group, 6 parents did not purchase the PRED following discharge due to “insufficient funds” and because “I forgot”. Only one parent in the DEX group failed to administer the second dose of DEX to their child. Significantly more children were excluded from enrollment in the PRED group than in the DEX group due to observed emesis in the ED.

Patients in both groups were found to be equivalent in demographics and severity of asthma upon presentation. Data reported from the children’s parents revealed no significant differences between oral beta-adrenergic agonists and inhaled corticosteroid use in the 24 hours preceding presentation to the ED. The number of nebulizer treatments administered in the ED was equal between groups. The total time spent in the ED and severity of asthma upon discharge did not differ (P values of 0.30, 0.09 and 0.35 for nebulizer use in ED, time in ED and severity of asthma upon discharge, respectively; all with a 95% CI). No significant difference in relapse rates between the two groups was found (DEX 7.4%, PRED 6.9%, OR of 1.08 and CI of 0.55 to 2.08 with P value of 0.84). DEX was found to be at least as effective in preventing relapse. There

was not a significant difference in admission in those who relapsed. An intention to treat analysis, considering relapse, favored the DEX group, however the difference was not of significant value (DEX 8.7%, PRED 13.5%, OR 0.61, CI 0.35 to 1.05, P of 0.07; NNT=200, ARR=-0.005). A larger amount of children in the PRED group missed 2 or more days of school, and their parents 1 or more days of work (19.5% vs 13.2%; P=0.05). The PRED group also had a higher rate of emesis at home (NNH=-50.0, ARI=-0.02), and fewer parents were compliant with administration of PRED at home, as measured by refills filled. Data from the intent to treat analysis is presented in Table 4.

The main adverse drug reaction to DEX was emesis, which was no greater than in those taking PRED. As detailed in the Qureshi group, days missed of work or school were found to be higher in the PRED group. None of the studies found a severe adverse reaction to DEX.

Table 2: Single dose DEX vs five day regimen of PRED

Study	P value	CER	EER	RRR	ARR	NNT	RRI	ARI	NNH
Altamimi	0.05	0.0179	0.0656	2.664	0.0477	21	-1	-0.01	-100

Table 3: Two day single dose DEX vs five day regimen of twice a day PRED

Study	P value	CER	EER	RRR	ARR	NNT	RRI	ARI	NNH
Greenberg	0.05	0.08	0.16	0.50	0.08	13	0.44	-0.08	-12

Table 4: Two day single dose DEX vs five day regimen of daily PRED

Study	P value	OR	CER	EER	RRR	ARR	NNT	RRI	ARI	NNH
Qureshi	0.07	1.08	0.074	0.069	-0.068	-0.005	200	-0.50	-0.02	-50

Discussion

PRED is the drug recommended for asthma exacerbations by the National Institutes of Health [9], and has been classically used despite an array of other corticosteroids being available. The half-life of PRED is 12 hours, necessitating a five-day regimen, often given twice daily, which inherently raises some compliance issues. Comparatively, the half-life of DEX is 36 to 72 hours, and it is approximately six times more potent than PRED. All three of the reviewed trials consistently showed DEX to be as effective as PRED, with a slightly lower rate of emesis, and an improved rate of parental compliance when measured. Furthermore, DEX administered at a dose of 0.6 mg/kg has been studied at length in the treatment of croup, without report of serious adverse drug reactions [11]. Regarding cost of medication, a study found that two days worth of DEX was more affordable for patients than five days worth of PRED, and use of DEX in acute asthma exacerbations also lead to decreased secondary costs [12]. Patients with compliance issues would theoretically do better with either a single or two-day, one time dose of DEX.

This review investigated a population aged 2-18 but not adult patients. It also did not investigate severe asthma exacerbations or those requiring intravenous steroids. The population size was relatively large in the Qureshi study but not so in the other two studies, and the Qureshi study was not double blinded.

Conclusion

This review showed that DEX is both safe and effective as a treatment modality for acute asthma exacerbations in children. The relapse rate within five to ten days was not significantly greater in those taking a one or two day regimen of DEX, compared to those taking a five day

regimen of PRED. Use of DEX may lead to better compliance and patient satisfaction [9]. Although more, larger studies would further elucidate the findings of this review, it may be reasonable to enact treatment with a one or two day regimen of DEX in asthma exacerbations, particularly in patients in which compliancy or affordability of medications is an issue.

Aside from larger studies, other pertinent issues warrant further examination. First, more studies examining a single dose of DEX would be helpful, as this is ideal in regards to patient compliance and satisfaction. Second, the long-term safety of DEX, especially in repeated doses to treat asthma in adolescents, should be examined. Finally, trials examining other patient populations and severities of asthma should be conducted. These could include the same treatment in adult patients, pregnant patients, patients with more severe presentations of asthma exacerbation, including those necessitating immediate airway interventions, and patients with a concurrent history of chronic heart, lung, liver or kidney disease.

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