

Clinical Communications

The use of a tapering dose of methylprednisolone for asthma exacerbations: Is it adequate?

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Clinical Implication

- A physician survey revealed that the use of a Medrol Dosepak for exacerbations of asthma is widespread. More appropriate doses of corticosteroids might lead to more rapid and complete resolution of exacerbations.

TO THE EDITOR:

Asthma is defined by the World Health Organization as a chronic disease that is characterized by recurrent attacks of breathlessness and wheezing that varies in severity and frequency from person to person.¹ To this generalized definition, it is also important to include individuals with asthma whose only symptom is cough.² The enormity of this problem results in asthma affecting approximately 300 million individuals of all ages, ethnic groups, and countries.³ It is estimated that approximately 250,000 people die prematurely each year as a result of asthma.³ In the United States, for the year 2009, 8.2% of the population (24.6 million people) had asthma. In 2007, there were 1.75 million asthma-related emergency department visits and 456,000 individuals with asthma who were hospitalized.⁴ Moreover, asthma was linked to 3447 deaths (approximately 9 per day) in 2007.⁴ The estimated cost in the United States was approximately \$56 billion for the treatment of individuals with asthma.⁵

Many individuals with asthma who have exacerbations (which consist of acute or subacute episodes of progressively worsening shortness of breath, coughing, wheezing, and chest tightness, or any combination thereof⁶) are pharmacologic failures; either the physicians did not give the patients an action plan, or the patient did not follow the directions for managing an increase in symptoms, which results in visits to physicians, urgent care facilities, or emergency departments and that results at times in hospitalizations and even fatalities. Acute asthma is usually precipitated by viral infections and/or exposure to allergens or irritants, eg, air pollution.⁷⁻¹¹ These triggers augment airway inflammation, airflow obstruction, and respiratory symptoms. Over the past 50 years, many randomized clinical trials have established corticosteroids as the cornerstone of anti-inflammatory therapy in adults who present to emergency departments or who are hospitalized for acute asthma.¹² The basis for corticosteroid treatment is derived from the concept that asthma has an inflammatory component besides the hyper-reactivity of the airway.¹³ Corticosteroids have been shown to reduce the inflammation, to improve pulmonary function tests, and to significantly decrease symptoms of cough, wheezing, and dyspnea. After an exacerbation of asthma has been brought under reasonable control, the Expert Panel Report (EPR) 2007 guidelines¹² strongly recommends that outpatients receive "bursts" of prednisone, from 40-60 mg in single or 2 divided doses for a total of 5 to 10 days in adults to reduce the risk of a recurrence. Similar

TABLE I. Pulmonary function tests

% of Predicted	Pre	Post*	1 Wk later
FVC	61	78	83
FEV ₁	54	72	85
FEF 25/75	30	46	73
Peak flow	65	81	90

FVC, Forced vital capacity; FEV₁, forced expiratory volume in 1 second; FEF 25/75, forced expiratory flow from 25% to 75% of vital capacity.

*After terbutaline and albuterol aerosol.

recommendations were made by Rowe et al,¹⁴ who recommended at least a 7- to 14-day course of prednisone. With this regimen, including inhaled corticosteroids, long-acting β -agonists and short-acting β -agonists, patients still relapsed. This is not surprising because, even when symptoms have resolved, evidence of inflammation in the airways may continue for up to 2 to 3 weeks.¹⁵

A Medrol Dosepak (MDP) (Upjohn Co, Kalamazoo, Mich) is a 6-day tapering course of methylprednisolone that begins with 24 mg on day 1, with a reduction by 4 mg per day over the next 5 days. Up to one-third of patients who initially respond to corticosteroid therapy with a larger dose than in the MDP relapse within the first 3 to 4 weeks after an emergency visit for an exacerbation of asthma, thus requiring increased medications, visits to emergency departments or to their physician, or even hospitalization.^{16,17} This communication presents a patient who is representative of the many individuals with asthma seen over the years whose symptoms did not resolve after using one or more MDPs.

R.S. is a 33-year-old woman with a history of intermittent coughing and wheezing for many years. She estimates that she is symptomatic approximately 50% of the time. She also develops dyspnea on exertion. Upper respiratory infections precipitate increased cough and wheezing, which have resulted in 4 emergency department visits in the past 4 years. Recently, she was treated with a budesonide/formoterol inhaler 160/4.5, 2 inhalations twice a day (b.i.d.), montelukast 10 mg once a day, and albuterol aerosol 1 to 5 times per day. At each emergency department visit, she was treated with an MDP, with a partial resolution of her symptoms. Although some days she was asymptomatic, she still had intermittent cough and wheezing. Allergic rhinitis and intermittent sinus headaches were additional problems, which were treated with a mometasone nasal spray, 2 sprays in each nostril b.i.d. There was no history of smoking. Four days before her visit, she developed an upper respiratory infection with increased cough and wheezing. On physical examination, she had swelling of the nasal turbinates. A chest examination revealed diffuse inspiratory and expiratory wheezes, with a marked amount of cough on forced expiration. She was treated with terbutaline subcutaneously and an aerosol with albuterol, with some decrease in the wheezing. There was still some cough with forced expiration. Pulmonary function tests were performed with a Puritan Bennett Spirometer (Wilmington, Mass); results are presented in Table I.

The patient was treated with prednisone 25 mg b.i.d. for 1 week and was continued on a budesonide/formoterol inhaler 160/4.5 2 inhalations b.i.d., montelukast 10 mg once a day, albuterol aerosol

TABLE II. The frequency of physicians using an MDP for an exacerbation of asthma

Always	Sometimes	Rarely	Never
28/237 (12%)	121/237 (51%)	40/237 (17%)	48/237 (20%)

3 to 5 times a day, and a mometasone nasal spray 2 sprays in each nostril once a day. R.S. was seen 1 week later. The cough and wheeze had resolved. On physical examination, her chest was now clear. There was no cough on forced expiration, and, as demonstrated, pulmonary function tests had improved. This patient, whose symptoms continued to persist with 4 separate MDPs had a total resolution of her symptoms with a dose of prednisone more consistent with the EPR 2007 guidelines.¹²

This communication also presents the results of a survey of physicians' prescribing habits regarding their use of an MDP in patients who have an exacerbation of asthma. A survey was sent to 430 physicians to determine their use of an MDP in their treatment of exacerbations of asthma; these included internists, family physicians, emergency department physicians, and hospitalists, who are all affiliated with the Cleveland Clinic or University Hospitals of Cleveland. The survey asked "if a patient presents to you with an exacerbation of asthma you: always, sometimes, rarely, or never prescribe an MDP." A card was enclosed that was returned anonymously (Table II).

Fifty-five percent of the physicians who received the survey responded. Sixty-three percent always or sometimes used the MDP for an exacerbation of asthma, whereas 37% rarely or never used the MDP for this situation. The survey revealed that a large number of patients are not being treated with an appropriate dose of corticosteroids, which possibly results in an unnecessary prolongation of their asthma symptoms.

The value of treating individuals with asthma with corticosteroids was first reported by Bordley et al.¹⁸ Fiel et al¹⁹ showed an advantage in giving oral corticosteroids to patients with attacks of asthma who were treated in emergency departments and subsequently sent home. This double-blind, controlled study of a short course of high-dose corticosteroids for outpatients reduced the relapse rate in symptoms after an acute asthma attack. The British Thoracic Society Guidelines in 1995 suggested 30-60 mg of prednisone for 7 to 21 days.²⁰ In 2002 Jones et al²¹ found that a 5-day course of 40 mg of prednisone per day may be sufficient for the majority of patients with exacerbations of asthma, provided the patient is protected by a medium-to-high dose of inhaled corticosteroids and supported by a self-management plan. The benefit of therapy with oral corticosteroids in reducing the number of relapses in patients with acute asthma is conclusive.²² The only study that remotely could be used to support an MDP, perhaps in patients with less-severe asthma, was a study by Chapman et al²² who treated patients discharged from an emergency department with 40 mg of prednisone for 2 days and then tapered to zero over the next 6 days. In the treatment group, 3 of 48 had a relapse, whereas 11 of 45 had a relapse in the placebo group. Thereafter (days 11 to 21), there was no further significant difference in relapse rates between treatment groups, 5 in the prednisone group and 6 in the placebo group.

It is not surprising that the patient presented in this report, treated with 4 MDPs, continued to have frequent symptoms after the exacerbation in spite of the use of inhaled corticosteroids. This is easily explained, because the amount of corticosteroids

presented in an MDP ranges from a minimum of 14% (84 mg/600 mg) to a maximum of 42% (84 mg/200 mg) of the dosage recommended by the EPR 2007 guidelines.¹² An MDP is totally inconsistent with these guidelines. Moreover, before determining that the patient is improving, the dosage in the MDP is decreased daily. This inappropriate dosage of corticosteroids may result in unnecessary and preventable return visits to the emergency department or to their physician because the symptoms have not resolved. The extent of the underuse of appropriate amounts of corticosteroids by physicians was shown by the survey response of 63% who always or sometimes used an MDP for treating exacerbations of asthma. The patient's expectation should result in almost total control.²³ Frequently, patients have a chronic cough, low-grade wheezing, and exercise-induced dyspnea without realizing that this is not necessary.

Moreover, the Medrol tablet package insert states that the dosage requirements of corticosteroids are variable and must be individualized on the basis of the disease under treatment and the response of the patient.²⁴ Although some patients may do reasonably well on this low dose of corticosteroids, this product clearly demonstrates an inherent contradiction. Similar problems were reported with an MDP that was used to treat rhus dermatitis (poison ivy), with relapses in the majority of patients who used it.²⁵

In conclusion, the survey of physicians who prescribe an MDP and the patient presented in this report highlight the significance of the underutilization of appropriate doses of corticosteroids in patients with an exacerbation of asthma. More appropriate use of higher doses might allow for the resolution of bronchial inflammation and might significantly ameliorate their symptoms and prevent frequent relapses, with fewer visits to their physician or emergency department, and improved quality of life. The convenience of taking a specific number of pills from a package each day might explain why this method evolved. Moreover, for the busy physician, it is simpler than specifying the exact number of corticosteroid pills that need to be taken. Compliance is an issue. Perhaps another type of dose pack could be developed, ie, an asthma prednisone dose pack with a dosage consistent with the EPR 2007 guidelines,¹² ie, 40-60 mg of prednisone a day. This more appropriate dose would provide the convenience of a dose pack while more closely reflecting the expert panel's recommendation of corticosteroids, with an increased chance of reducing symptoms and thus preventing future relapses, improving quality of life, and leading to a significant decrease in medication costs. A survey of 6 pharmacies, 5 national chains, and a local pharmacy revealed that if ten 20-mg tablets of prednisone were prescribed (40 mg per day for 5 days) instead of an MDP, then there would be a 70% reduction in cost. Except for the individuals with the mildest asthma, the MDP should probably not be prescribed because (a) it contains a dose that is not even closely consistent with the EPR 2007 guidelines¹² on corticosteroid dosage, (b) the dose is tapered immediately on day 2 before one even knows that the patient is improving, (c) there is a significant increase in cost versus prednisone for 5 days, and (d) there is no need to take this medication 3 times a day. Finally, this report highlights the frequency of the use of an MDP in our community for patients with asthma who have exacerbations. A randomized parallel group study, in which one group is treated with the EPR 2007 guidelines¹² recommended dose of corticosteroids and the other is treated with an MDP would be necessary to confirm the superiority of the higher dose of prednisone in leading to the resolution of asthma exacerbations.

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