

The current place of nedocromil sodium in the treatment of asthma

Romain Pauwels, MD, PhD Ghent, Belgium

Current guidelines for the treatment of asthma are based on the fact that asthma is an inflammatory disease and that all forms of persistent asthma, whether mild, moderate, or severe, require treatment with a controller medication to reverse or prevent the underlying inflammation. A patient can be considered to have mild persistent asthma if symptoms occur one or more times a week (but less than daily), if exacerbations are affecting activity or sleep, if nighttime symptoms occur more than twice a month, or if peak expiratory flow or FEV₁ is equal to or greater than 80% of the predicted value or has a variability of 20% to 30%. Just one of these clinical features is needed to define the condition. A patient with this condition should be treated with a controller medication that is taken daily; the physician may choose between a low dose of inhaled corticosteroid, nedocromil sodium or cromolyn sodium, or slow-release theophylline. The choice will vary depending on the physician and the type of patient being treated. Data on clinical efficacy and safety support the current position of nedocromil sodium as a primary treatment for mild persistent asthma. (J Allergy Clin Immunol 1996;98:S151-6.)

Key words: Asthma, nedocromil sodium, treatment guidelines

At present, inhaled nedocromil sodium is one of four "controller" medications recommended for the treatment of mild, persistent asthma. This is the recommendation of the newest of the international guidelines on asthma management, Global Initiative for Asthma (GINA),¹ a joint initiative of the National Heart, Lung, and Blood Institute and the World Health Organization. Many of the recommendations in this publication are based largely on those of an earlier report, the International Consensus Report on Diagnosis and Management of Asthma,² which was published some 3 years ago, while also being adapted to meet the needs of a wider global community. Particular emphasis has been put on the role of airway inflammation in the pathogenesis of asthma, the importance of control and prevention in treatment, and the need to identify risk factors for the development of asthma. Thus asthma treatment is predicated on medications to reverse and prevent the inflammatory process.

The choice of treatment for asthma is guided by

Abbreviations used

GINA: Global Initiative for Asthma
PEF: Peak expiratory flow

the classification of the severity of the disease and, conversely, treatment requirements are a guide to severity. Given this degree of interdependence, this article will briefly review the classifications of asthma severity and describe the positioning of nedocromil sodium within this classification.

GOALS OF ASTHMA MANAGEMENT

To avoid placing undue emphasis on the pharmacologic treatment of asthma, it is necessary to remember that asthma management has six interrelated, and arguably equally important, parts:

1. Educating patients to develop a partnership in asthma management
2. Assessing and monitoring asthma severity with measurements of symptoms and measurements of lung function
3. Avoiding or controlling asthma triggers (non-pharmacologic secondary prevention)
4. Establishing medication plans for long-term management

From the Department of Respiratory Diseases, University Hospital, State University of Ghent, Belgium.

Reprint requests: Romain Pauwels, MD, PhD, Department of Respiratory Diseases, University Hospital, State University of Ghent, De Pintelaan 185, B9000 Ghent, Belgium.

Copyright © 1996 by Mosby-Year Book, Inc.
0091-6749/96 \$5.00 + 0 1/0/76621

TABLE I. Step 1: Intermittent asthma

Clinical features before treatment*	Medication required to maintain control
Intermittent symptoms <1 time/wk Brief exacerbations Nighttime symptoms <2 times/mo Asymptomatic and normal lung function between exacerbations PEF or FEV ₁ ≥80% predicted Variability <20%	Intermittent reliever medication taken as needed only; inhaled short-acting β_2 -agonist Intensity of treatment depends on severity of exacerbation (oral corticosteroids may be required)

*The presence of any one of the features described within a category is sufficient to place a patient within that category.

TABLE II. Step 2: Mild persistent asthma

Clinical features before treatment*	Daily medication required to maintain control
Symptoms ≥1 time/wk but <1 time/day Exacerbations may affect activity and sleep Nighttime symptoms ≥2 times/mo PEF or FEV ₁ ≥80% predicted Variability 20% to 30%	One daily controller medication; possibly add a long-acting bronchodilator to antiinflammatory medication (especially for nighttime symptoms)

*The presence of any one of the features described within a category is sufficient to place a patient within that category.

5. Establishing plans for managing exacerbations

6. Providing regular follow-up care

Although there is no cure for asthma, appropriate management can often control the disease. Thus the goals of management are to achieve and maintain control of symptoms, prevent asthma exacerbations, maintain pulmonary function as close to normal as possible, maintain normal activity levels, including exercise, avoid adverse effects from asthma medications, prevent development of irreversible airflow limitation, and prevent asthma mortality. These goals reflect the fact that asthma is a chronic disorder with progressively developing chronic airway inflammation leading to recurrent episodes of such airway responses as airflow limitation, mucus production, and cough.

MEDICATION PLANS FOR LONG-TERM ASTHMA MANAGEMENT

Numerous clinical studies have shown that any asthma more severe than mild, intermittent asthma is more effectively controlled by intervening to suppress (or reverse) the inflammation rather than by only treating the bronchoconstriction and related symptoms. Thus we can classify medications as "controllers" or "relievers." In persistent asthma, whether mild, moderate, or severe, the reliever medication is a short-acting inhaled β_2 -agonist (preferred) or other type of short-acting bronchodilator. Controller med-

ications include corticosteroids, inhaled or oral, cromolyn sodium, nedocromil sodium, sustained-release theophylline, and long-acting bronchodilators. The preferred combination of treatments varies according to asthma severity.

Intermittent asthma

Intermittent asthma is not trivial. Although it is rarely life threatening, the severity of the exacerbation may vary over time and between patients (see Table I). The management of exacerbations is outside the scope of this review, but for patients whose asthma is precipitated by a specific trigger such as allergen or exercise, treatment includes medication as needed before exercise (inhaled β_2 -agonist, cromolyn sodium, or nedocromil sodium) or allergen exposure (cromolyn sodium or nedocromil sodium).

Mild persistent asthma

It is important to note that GINA recommends the daily use of a controller (antiinflammatory) medication for mild persistent asthma (see Table II). The choices for the daily controller medication are as follows (the preferred treatments are in bold print):

- Either **inhaled corticosteroid, 200 to 500 μ g, cromolyn sodium, nedocromil sodium**, or sustained-release theophylline.

TABLE III. Step 3: Moderate persistent asthma

Clinical features before treatment*	Daily medication required to maintain control
Symptoms daily Exacerbations affect activity and sleep Nighttime symptoms >1 time/wk PEF or FEV ₁ >60% to <80% predicted Variability >30%	Daily controller medications: inhaled corticosteroid and long-acting bronchodilator (especially for nighttime symptoms)

*The presence of any one of the features described within a category is sufficient to place a patient within that category.

TABLE IV. Step 4: Severe persistent asthma

Clinical features before treatment*	Daily medication required to maintain control
Continuous symptoms Frequent exacerbations Frequent nighttime symptoms Physical activities limited by asthma symptoms PEF or FEV ₁ ≤60% predicted Variability >30%	Multiple daily controller medications: high-dose inhaled corticosteroid, long-acting bronchodilator, and oral corticosteroid long term

*The presence of any one of the features described within a category is sufficient to place a patient within that category.

If needed, increase inhaled corticosteroids (up to 800 µg), or add a long-acting bronchodilator (especially for nighttime symptoms)—a long-acting oral or inhaled β_2 -agonist or sustained-release theophylline.

Children should usually be given an initial trial (4 to 6 weeks) of cromolyn sodium. If the patient's long-term therapy was initiated with nedocromil sodium, cromolyn sodium, or sustained-release theophylline and symptoms persist after 4 weeks of this initial treatment, then inhaled corticosteroids should be introduced, either instead of or together with the other medication, to allow an overlap period.

The recommended reliever medication is a short-acting inhaled β_2 -agonist to be used as needed for symptoms but not to be used more than 3 or 4 times a day.

Moderate persistent asthma and severe asthma

The remaining classifications of asthma severity and recommended treatments are described in Tables III and IV. The preferred controller medication for moderate persistent asthma is an inhaled corticosteroid in the dose range 800 to 2000 µg/day. The recommendations for reliever medication are the same as for mild persistent asthma.

For severe asthma, the reliever medication is a short-acting inhaled β_2 -agonist as needed for symptoms.

STEPPING UP AND DOWN

If control is not being achieved, the first action to take is to review the patient's technique for use of medication, compliance, and environmental control; if these are optimal, an increase in medication should be considered.

It is important to remember that the stepwise approach to the pharmacologic management of asthma incorporates the concept of stepping down as well as stepping up. Thus treatment should be reviewed every 3 to 6 months and, if control has been sustained for at least 3 months, a gradual stepwise reduction in treatment may be possible. The aim of treatment is, of course, to control asthma, which may be defined (at whatever step of asthma severity) as including the following:

- Minimal (ideally no) chronic symptoms, including nocturnal symptoms; minimal (infrequent) episodes
- No emergency visits
- Minimal need for as required β_2 -agonist
- No limitation on activities, including exercise

TABLE V. Asthma treatment modalities in mild persistent asthma

Drug	Control of chronic symptoms over weeks to months	Potential for serious side effects long term
Inhaled corticosteroids	+++	+
Cromolyn sodium	++	—
Nedocromil sodium	++	—
Sustained-release theophylline	+	++
Long-acting oral β_2 -agonist	+/-	+
Ketotifen	+ (Applies to children)	—

- Peak expiratory flow (PEF) circadian variation <20%
- (Near) normal PEF
- Minimal (or no) adverse effects from medication

The stepwise approach is necessary to identify the minimum therapy required to maintain control. This will help to reduce the risk of side effects and enhance patient adherence to the treatment plan.

Children

One of the reasons why children need special consideration is that they are more vulnerable to the risk of side effects. Thus systemic absorption of high doses of inhaled corticosteroids is a potential concern because of their possible effect on linear growth.³ When inhaled corticosteroids are substituted or added to treatment with nedocromil sodium or cromolyn sodium to achieve control of asthma, an appropriate step down to consider is gradually reducing the inhaled corticosteroids and maintaining control with nedocromil sodium or cromolyn sodium. The inhaled corticosteroid may need to be restarted for seasonal asthma.

NEDOCROMIL SODIUM

Nedocromil sodium is classified as a controller medication to be used daily on a long-term basis to achieve and maintain control of persistent asthma. Other medications in this category are inhaled and systemic corticosteroids, cromolyn sodium, sustained-release theophylline, and long-acting inhaled and oral agonists. Possibly, ketotifen and other antiallergics and various other experimental compounds may be included. Inhaled corticosteroids are at present the most effective controller medications.

Nedocromil sodium is described in GINA as follows:

Mode of administration. Inhaled.

Mechanisms of action. In in vitro and in vivo studies in animal and human models of asthma, this antiinflammatory pyranoquinolone is 4 to 10 times more potent than sodium cromoglycate in preventing induced bronchoconstriction in animal models of asthma and in humans.^{4,5} Although the precise mechanism of action is not fully understood, it has been shown that nedocromil sodium inhibits activation of and mediator release from several types of inflammatory cells. It also inhibits neuronal pathways. No long-term effect on the chronic inflammatory changes in asthma has yet been demonstrated.

Role in therapy. As with sodium cromoglycate, this medication may be used as maintenance therapy early in the course of asthma. Clinical trials in adult patients with asthma show that therapy with nedocromil sodium has a rapid effect on symptoms, improves lung function, and reduces nonspecific airway responsiveness.⁶⁻⁸ Clinical trials with nedocromil sodium are ongoing in childhood asthma and show an efficacy similar to that in adults.⁹

Side effects. Treatment with nedocromil sodium is not associated with any significant adverse effects.

This description from GINA is based on the results of several carefully controlled clinical trials. In a meta-analysis performed on all controlled clinical trials, stratified according to baseline therapy (and thus, approximately, to severity of asthma),¹⁰ nedocromil sodium appeared to be most effective when added to or substituting for bronchodilator treatment, which accords with its position in the GINA guidelines as a recommended daily treatment for mild persistent asthma.

The choice of initial controller treatment for mild persistent asthma is obviously governed by efficacy and the risk of side effects. Table V compares nedocromil sodium with the other med-

ications available for treating mild persistent asthma. The perception of this balance, however, might differ between individual physicians and between the types of patients each physician is seeing.

The future role of nedocromil sodium

Guidelines are not static documents but need to evolve as new information becomes available on all aspects of asthma. This includes recommendations on treatment modalities, which are always open to change with the introduction of new drugs and new clinical data. One area that needs further research is early or intermittent asthma and whether early therapeutic intervention at this point might alter the natural history of the disease. In moderate asthma, more studies might also be done to investigate the effect of different combinations of drugs.

REFERENCES

1. National Heart, Lung, and Blood Institute. Global initiative for asthma: global strategy for asthma management and prevention [NHLBI/WHO report]. Bethesda (MD): National Institutes of Health; 1995 Jan. Publication No.: 95-3659.
2. National Heart, Lung, and Blood Institute. International consensus report on diagnosis and management of asthma. Bethesda (MD): National Institutes of Health; 1992 June. Publication No.: 92-3091.
3. Doull IJM, Freezer NT, Holgate ST. Growth of children with mild asthma treated with inhaled beclomethasone dipropionate. *Am J Respir Crit Care Med* 1995;151:1715-9.
4. Auty RM, Holgate ST. Nedocromil sodium: a review of its anti-inflammatory properties and clinical activity in the treatment of asthma. In: Kay AB, editor. *Allergy and asthma: new approaches to therapy*. Oxford: Blackwell Scientific, 1989.
5. Busse WW, Orr TSC, Pauwels R. Proceedings of an international symposium on nedocromil sodium, 1988 June 13-15, Paris. *Drugs* 1989;37(suppl):1-137.
6. Cherniack RM, Wasserman SI, Ramsdell JW, Selner JC, Koepke JW, Rogers RM, et al. A double-blind multicenter group comparative study of the efficacy and safety of nedocromil sodium in the management of asthma. *Chest* 1990;97:1299-306.
7. Bel EH, Timmers MC, Hermans J, Dijkman JH, Sterk PJ. The long-term effects of nedocromil sodium and beclomethasone dipropionate on bronchial responsiveness to methacholine in nonatopic asthmatic subjects. *Am Rev Respir Dis* 1990;141:21-8.
8. Thomson NC. Nedocromil sodium: an overview. *Respir Med* 1989;83:269-76.
9. Armenio L, Baldini G, Bardare M, Boner A, Burgio R, Cavagni G, et al. Double blind, placebo controlled study of nedocromil sodium in asthma. *Arch Dis Child* 1993;68:193-7.
10. Edwards AM, Stevens MT. The clinical efficacy of inhaled nedocromil sodium (Tilade) in the treatment of asthma. *Eur Respir J* 1993;6:35-41.

DISCUSSION

P. König. I think you need to separate children from adults. The side effects of inhaled steroids in relatively small doses are much less of a problem in adults than the potential growth suppression in children with mild asthma in the long term, which is now fairly well documented by the studies by Doull and Tinkelman. In terms of efficacy, in children with mild asthma, two out of three studies showed equal efficacy of cromolyn sodium and inhaled steroids. In response to your suggestion that we might try intervention in patients with intermittent asthma, we have recently concluded a long-term study following up on our own patients for up to 16 years. We divided the patients into those with mild asthma, which would be about the same as your intermittent group, who were treated with as-needed bronchodilators only; those with moderate asthma, treated with cromolyn sodium; and those with severe asthma, treated with inhaled steroids. The two groups treated with antiinflammatories, cromolyn sodium, and inhaled steroids improved both in pulmonary function and in their clinical situation over the years. The only group that worsened in many respects, certainly in pulmonary function, was the group with mild asthma, which was treated with adrenergic agents only; this occurred despite the fact that previous studies looking at the long-term natural course of the disease have all said that patients with severe asthma tend to have a worse prognosis in the long term than do patients with mild asthma. You are very right in saying that we ought to do long-term studies of continuous antiinflammatory treatment in mild asthma and see what happens.

R. Pauwels. I took into account the difference between children and adults by saying that the perception of the possibility of side effects will differ from physician to physician and between patient groups.

J. M. FitzGerald. I think it is misleading to show a table with serious side effects against a 500 to 1000 μ g dose of inhaled corticosteroids. One of the most important things we want to do in asthma is to prevent asthma mortality. Ernst's data from Saskatchewan show that at those doses there is a preventative effect in terms of asthma mortality, and that has to be put into the equation. The other issue that has to enter our discussions on therapeutic interventions is the fact that combination therapy is expensive. If we have a patient who is taking 500 to 1000 μ g beclomethasone, it makes sense to add nedocromil sodium or salmeterol from the point of view of therapeutic efficacy, but we have to be concerned in terms of compliance and the patient's acceptance of treatment. For example, if you were a patient who had been given salmeterol on top of inhaled steroids and after 2 months' therapy you were deciding which drug you would continue, you might well end up continuing with salmeterol. Important public health policy issues and costs of drugs should be included in our discussions.

R. Pauwels. The points you raise are correct and could be the subject of a separate workshop, but one of the

answers to combination therapy would be to put the two drugs in the same aerosol.

J. P. Seale. If I understood Peter König correctly, he has very important long-term data over 15 or 20 years in relation to what is called minimal disease. Are they recent data, or have they been published? I ask because when Romain Pauwels was suggesting that treating what he calls intermittent disease with something other than β -agonists might stop its progression to something more troublesome, I did not know that such data on natural history were available.

P. König. They are recent and have been published only as an abstract, presented at last year's ERS meeting. The full paper has not yet been published.

R. Beasley. Can you remind us of the treatment recommendations for intermittent asthma?

R. Pauwels. Use cromolyn or nedocromil sodium or β -agonists before certain triggers such as exercise or allergen exposure, but on an as-needed basis. This recommendation was well debated and takes into account the fact that we do not have the data to make any firm recommendations. Another consideration is that the degree of compliance you can expect from patients who have intermittent symptoms or unperceived symptoms is going to be very low.

P. J. Barnes. If people have episodic asthma, are you suggesting they should have cromolyn or nedocromil sodium only at the time they are symptomatic and not when they are asymptomatic? This seems very reasonable.

R. Pauwels. No, the current recommendation is that if a person has intermittent asthma—for example, somebody who has occasional exercise-induced asthma but is completely symptom-free and has a normal lung function in between—they should take either a short-acting β -agonist or nedocromil sodium or cromolyn before the exercise.

P. J. Barnes. And do you think that is right?

R. Pauwels. We should look much more carefully at this type of subject and study the natural history. As

Peter König's data would suggest, that might be a good category for intervention to prevent the development of persistent asthma.

J. Ch. Virchow. Peter Barnes raised a point a while ago about the time course of action of nedocromil sodium and maybe cromolyn sodium. In Germany, most cromolyn sodium is marketed in a combination with the β -agonist reproterol. When we are strictly following the guidelines and we have patients who need their bronchodilator only once or twice a week, if they have it in the form of this combination then we switch them to β -agonists alone, because we say it is no use to take cromoglycate just once a week or as needed. I would be interested in your view on what we should do.

R. Pauwels. I am not aware of any data supporting the combination preparation of a short-acting inhaled β -agonist and nedocromil sodium or cromolyn sodium. We should be suspicious about such a combination in view of the data that were presented yesterday.

J. Ch. Virchow. Are you suggesting then that if we switch them to β -agonist alone we are doing the right thing?

R. Pauwels. You should leave out the short-acting β -agonist. Studies that have looked at compliance, for example, because that could be a motivation, show that adding a short-acting β -agonist to nedocromil sodium does not enhance compliance at all.

J. Ch. Virchow. Yes, but I have teenage patients who have intermittent asthma once a week when they play soccer, for instance. They use the combination cromolyn sodium and reproterol once before they play soccer, and have no problems for the rest of the week. Next week they use it again. I cannot persuade these patients to take cromolyn sodium or nedocromil sodium four times a day, 7 days a week. It would not be reasonable.

R. Pauwels. No, unless it is shown—and these are the studies that need to be done—that we can prevent the development of a more serious disease.