

The effects of cromolyn sodium and nedocromil sodium in early asthma prevention

Peter König, MD, PhD *Columbia, Mo*

The possibility of irreversible obstruction and therefore the need for early intervention is being much debated. Some investigators suggested that delay in starting inhaled corticosteroids will result in irreversible obstruction. Our own long-term study, specifically designed to detect irreversible obstruction showed that a step-wise approach (starting with cromolyn sodium and switching to inhaled corticosteroids if clinical control and pulmonary function tests are not satisfactorily controlled) resulted in an increase in pulmonary function and not a deterioration. There was no evidence that a delay in starting inhaled corticosteroids will result in irreversible obstruction or clinical worsening. However, delay in starting cromolyn sodium in patients treated with bronchodilators alone did result in worsening pulmonary function tests and worse clinical outcomes. One study from Finland and another study from Australia came to the same conclusion. Even though some studies with cromolyn sodium did not show benefit in the first year of life, other studies did show a good response. The choice between nonsteroidal drugs, such as cromolyn sodium and inhaled corticosteroids as first-line drugs, has to be made on the risk/benefit ratio of these drugs. Although in severe asthma inhaled corticosteroids have greater efficacy, in mild-to-moderate asthma there is comparable efficacy, and the nonsteroidal drugs have better safety. A step-wise approach is still a logical approach (*J Allergy Clin Immunol* 2000;105:S575-85.)

Key words: Early intervention, asthma, cromolyn sodium, nedocromil sodium, irreversible obstruction, long-term outcome

The idea of early intervention in asthma seems to be more frequently debated in the last few years. Considering the importance of inflammation in asthma, any pharmacologic early intervention should be done with anti-inflammatory drugs.

The first question that needs to be addressed is why one would consider early intervention: to prevent asthma from occurring at all (primary prophylaxis)—an exciting concept, but no data exists about pharmacologic means being able to achieve this goal; and to improve the long-term prognosis of asthma and perhaps to prevent the occurrence of irreversible airway obstruction.

The second question that needs to be addressed is how early intervention should be performed. There are 2 possible approaches: (1) Early intervention after the onset of the disease has been mostly advocated by investigators

who proposed that in the absence of treatment with inhaled corticosteroids, childhood asthma has a progressive downhill course that results in the development of irreversible airway obstruction.¹ (2) Anti-inflammatory drugs should be started in patients with milder asthma than those suggested by earlier guidelines.²⁻⁴ Studies of the natural history of childhood asthma agree on some basic facts: One is that a substantial proportion of children who wheeze in the first few years of life will stop wheezing (28%-43%).^{5,6} The same studies also agree that severe disease is an important risk factor for chronicity in the long term.^{5,6}

A few studies have examined the possibility whether drug therapy can affect the long-term prognosis. Martin et al⁶ followed 371 children and evaluated them at age 7, 10, 14, and 21 years. They concluded that adequacy of treatment did not have an effect on the long-term outcome. However, anti-inflammatory drugs became available relatively late in their follow-up. Thus cromolyn sodium became available in Australia after the 10-year check-up, and inhaled corticosteroids became available only after the 14-year visit. In addition, the authors definition of *adequate treatment* was cromolyn sodium or maintenance adrenergic agents. The latter is not considered appropriate treatment in the absence of anti-inflammatory drugs in the recent guidelines.²⁻⁴

In a study from Finland, Kokkonen and Linna⁷ monitored 108 patients with asthma from childhood to ages 20 to 24 years. Sixty percent of these patients were treated with as-needed bronchodilators; 20%, with cromolyn sodium; and 20%, with inhaled corticosteroids. These authors also concluded that drug therapy had no effect on the long-term outcome. Unfortunately, no explanation is given in the paper about the indications for these drugs; therefore no inferences can be made about the current indications of these drugs.²⁻⁴ There is, in fact, some suggestion in their results that anti-inflammatory drugs might have an effect on the long-term outcome. Thus anti-inflammatory drugs were given to 70% of patients whose condition improved but only to 45% of those patients whose condition worsened.

All the guidelines²⁻⁴ recommended that in children, anti-inflammatory drugs in the form of cromolyn sodium should be started at the level of moderately severe asthma, and inhaled corticosteroids should be used in patients with severe asthma, whose condition could not be controlled by cromolyn sodium.

In 1994, Agertoft and Pedersen¹ published a study of budesonide that was given to children with mild-to-mod-

From the Department of Child Health, University of Missouri.
Reprint requests: Peter König, MD, PhD, Child Health, M659, University of Missouri, One Hospital Dr, Columbia, MO 65212.
Copyright © 2000 by Mosby, Inc.
0091-6749/2000 \$12.00 + 0 1/0/99976

erate asthma for 3 to 6 years, compared to a control group. They found that the annual increase in FEV₁ in the budesonide group was significantly greater in patients in whom the onset of the disease was less than 2 years before start of the steroid therapy, compared with those in whom the onset was more than 5 years earlier. In the control group, an annual decrease in predicted FEV₁ value of 1% to 3% was measured. From this they suggested that perhaps delay in starting inhaled corticosteroids can cause irreversible airway obstruction.

There are several problems with these conclusions:

1. The study was not designed to investigate irreversible airway obstruction. The results represent a prebronchodilator baseline; no postbronchodilator results are given, and no short course of systemic steroids was attempted; therefore the authors really cannot say whether the obstruction was irreversible because they made no attempt to reverse it.
2. The control group was much smaller than the treatment group, and it was not randomly selected but included patients who refused corticosteroid therapy (steroid-phobic).
3. All patients received maintenance adrenergic therapy with terbutaline. According to some studies, this can cause worsening of clinical control and pulmonary function test^{8,9} in asthma and can increase late allergic reaction.¹⁰

This study generated a line of thought that assumed that childhood asthma, in the absence of inhaled corticosteroid therapy, has a progressive downhill course, resulting in irreversible obstruction. This hypothesis, if true, would strongly support early intervention soon after the onset of the disease and would mandate the use of inhaled corticosteroids as the only choice of anti-inflammatory treatment.

To test this hypothesis, we conducted a retrospective study of 175 children with asthma who were treated in a step-wise manner, very similar to that of the guidelines.² The study was designed to test the hypothesis that irreversible obstruction occurs with delay in starting inhaled corticosteroids and was mostly aimed at examining the long-term outcome of the step-wise approach.² The patients were followed on average for 8.4 years (range, 2.2-16.8 years). The data were based on chart review, end-of-study questionnaire, and spirometry.¹¹ To test the reversibility of any degree of obstruction, at the end of the study all patients were given albuterol, and spirometry was measured both before and after the treatment.

The original classification by severity, at the start of the study, was mild (patients symptomatic on 3 or less days per week), moderate (patients symptomatic on more than 3 days per week), or severe. In patients old enough to perform spirometry, this was performed at every clinic visit, and the results were included in the decision-making process on the appropriate classification and therapy. The patients with mild disease were treated with "as needed" bronchodilators; the patients with moderate disease were treated with cromolyn sodium, and the patients with severe disease (defined as not controlled by

cromolyn sodium) were treated with inhaled corticosteroids.²

If, during the follow-up, the severity of the disease changed, the treatment was stepped up or down, accordingly; therefore at the end of the study, many patients were on different treatment from the original regimen.

The final clinical outcome showed that about 15% of patients were free of symptoms for at least 1 year, on no asthma medication. There was no significant difference between the 3 original groups of severity in terms of the proportion that became asymptomatic. This is different from what one would expect from the natural history of the disease, which is for the patients with more severe disease to be less likely to "outgrow" their asthma.^{5,6}

Approximately one half of the patients treated with anti-inflammatory drugs (cromolyn sodium or inhaled corticosteroids) improved sufficiently to move to a milder group, although only 17% of the original mild group did so (Fig 1). The proportion of patients whose condition remained the same or worsened was significantly higher in the mild group, treated with bronchodilators-only compared with either the cromolyn sodium or the inhaled steroid group.

Delay in starting cromolyn sodium was 14.3 months in the patients whose condition remained the same or worsened but only 1.3 months in the patients whose condition improved; this difference was statistically significant. The respective numbers for delay in the start of inhaled corticosteroids were 20 and 18.7 months, and the difference was not significant. Thus it seems that the important step is to start anti-inflammatory drugs, but it does not have to be inhaled corticosteroids.

The best pulmonary function tests were in the mild group at the start of the study; but at the end of the study, the original moderate group had the best results. Even the original severe group had better results than the mild group in 2 of 3 spirometric tests (Fig 2). The results of the moderate group, started on cromolyn sodium, improved from start to end and were quite normal. Final pulmonary function tests were affected positively by treatment with cromolyn sodium and inhaled corticosteroids and negatively affected by a delay in starting cromolyn sodium but not inhaled corticosteroids. There was no significant effect of age at onset or duration of asthma.

When changes from start to end (end of study or point at which treatment was changed) within the original treatment regimens were analyzed, it was found that the group treated with bronchodilators only had a significant worsening in pulmonary function, that those treated with cromolyn sodium experienced no change, and those treated with inhaled corticosteroids had a trend for improvement, which reached statistical significance on forced vital capacity (Fig 3).

This study does not support the hypothesis that childhood asthma, in the absence of inhaled corticosteroids, has a progressive downhill course, resulting in irreversible airway obstruction. The evidence shows that both anti-inflammatory drugs (cromolyn sodium and

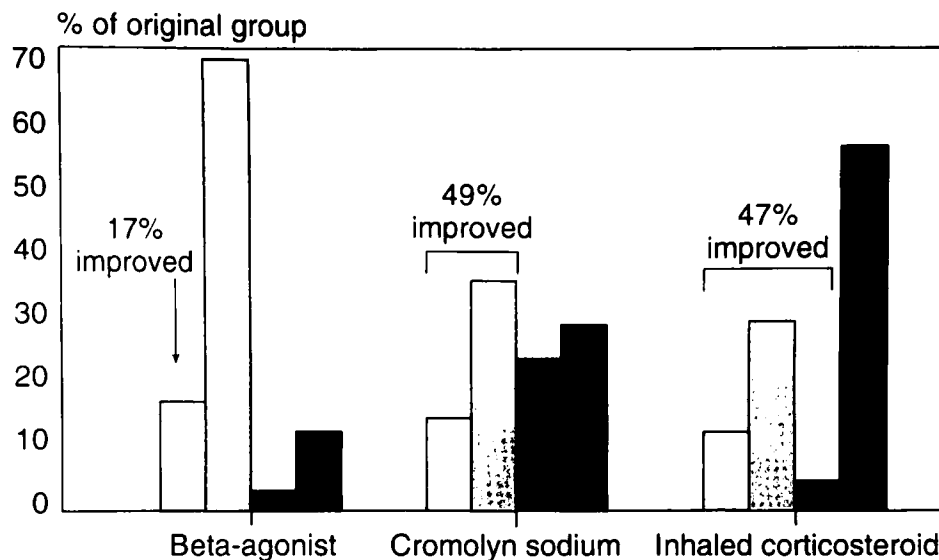


FIG 1. Asthma severity classifications at end of the study. Severity categories are shown according to the original 3 treatment groups (as needed: β -agonist, mild asthma; cromolyn sodium, moderate asthma; inhaled corticosteroids, severe asthma). *Open bars* represent patients who were free of symptoms (not receiving any antiasthma medications); *light gray bars* represent patients with mild asthma (treated with bronchodilators only, as needed); *dark gray bars* represent patients with moderate asthma (treated with cromolyn sodium); *black bars* represent patients with severe asthma (treated with inhaled corticosteroids). (From König P, Shaffer J. The effect of drug therapy on long-term outcome of childhood asthma: a possible preview of the international guidelines. *J Allergy Clin Immunol* 1996;98:1103-11. By permission.)

Final pulmonary function test

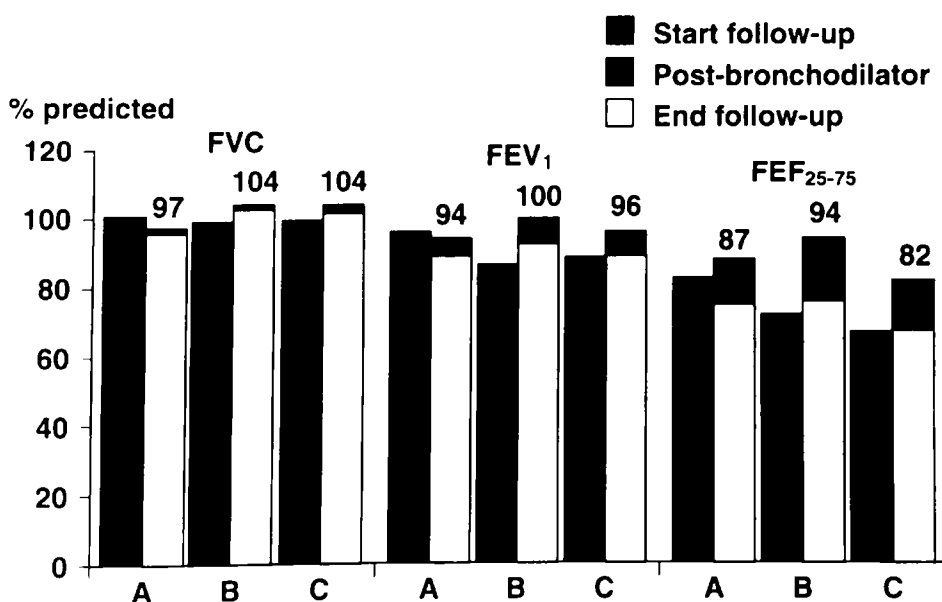


FIG 2. Pulmonary function tests at start and end of follow-up. FVC, Forced vital capacity; FEF₂₅₋₇₅, forced expiratory flow; A, mild asthma (bronchodilators, as needed); B, moderately severe asthma (cromolyn sodium); C, severe asthma (inhaled corticosteroids). (Modified from König P, Shaffer J. The effect of drug therapy on long-term outcome of childhood asthma: a possible preview of the international guidelines. *J Allergy Clin Immunol* 1996;98:1103-11. By permission.)

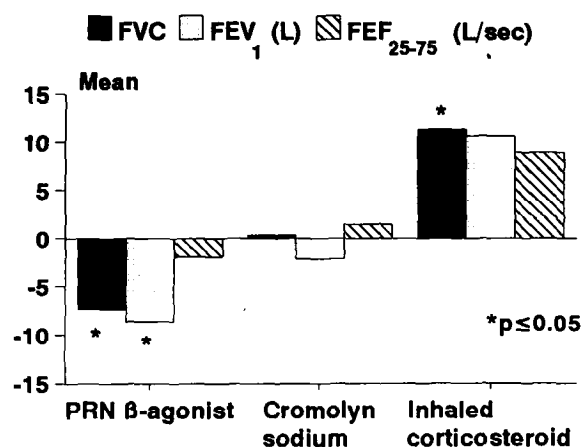


FIG 3. Change in pulmonary function from start to end of initial treatment with either β -agonists, sodium cromolyn, or inhaled corticosteroids. All values are prebronchodilator use. FVC, Forced vital capacity; FEF₂₅₋₇₅, forced expiratory flow; PRN, as needed. (From König P. Evidence for benefits of early intervention with non-steroidal drugs in asthma. *Pediatr Pulmonol* 1997; 15(suppl):34-9. Copyright 1997. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

inhaled corticosteroids) are disease-modifying agents and at least partially reversed the natural history of the disease, which is for the patients with mild asthma to experience better results than the patients with more severe asthma, although the opposite was true in this study. It seems that the crucial step is the jump from bronchodilators to an anti-inflammatory drug, and this can be cromolyn also, not necessarily inhaled steroids.

The step-wise approach, on the whole, had a positive long-term outcome. However, the initiation of cromolyn sodium therapy, as defined by those guidelines,² may be too late; and starting cromolyn in patients with milder disease could further improve the long-term outcome.

Even though it may be argued that this study was retrospective,¹¹ while the study by Agertoft and Pedersen¹ was prospective, it is also true that the first was specifically designed to look for irreversible obstruction and had a much longer follow-up¹¹ than the Danish study.¹

A cross-sectional study of Finnish school children,¹² managed according to the same guidelines² as our study,¹¹ came to very similar conclusions. They treated the patients with mild disease with "as needed" bronchodilators, the patients with moderately severe disease with cromolyn sodium or nedocromil sodium, and the patients with severe disease with inhaled corticosteroids. They also found the best pulmonary function results in the moderate group, and the difference reached statistical significance compared with the mild group on peak expiratory flow rate and FEV₁ value and compared with the severe group on peak expiratory flow rate. They also concluded that the initiation of nonsteroidal inhaled anti-inflammatory drugs in patients with milder disease than the recommendations of the guidelines² might benefit some patients.

Oswald et al¹³ followed a group of children from 7 to

35 years old, for a total of 28 years. They were also testing the hypothesis that the lack of treatment with inhaled corticosteroids will result in irreversible obstruction; they found no evidence to support this hypothesis.

Some studies with cromolyn sodium suggested that it may not work in the first year of life, thus making it a questionable candidate for intervention early after onset of the disease.^{14,15} On the other hand, Henry et al,¹⁶ in a group of children under 2 years of age, found that, even though the cromolyn responders tended to be older, some children under 1 year were clearly responders.

Yüksel and Greenough¹⁷ treated a group of premature infants and children aged 4 to 31 months. They showed significantly fewer symptoms and bronchodilator use with cromolyn sodium compared with placebo and concluded that cromolyn responsiveness did not correlate with either gestational or postnatal age. The same authors performed a similar study with nedocromil sodium with the same positive results.¹⁸

Reijonen et al¹⁹ studied a group of children under 2 years of age who had bronchiolitis. The patients were treated for 4 months with cromolyn sodium or budesonide and compared with a group who were receiving no therapy. The number of children with at least 1 subsequent wheezing episode was significantly lower in both anti-inflammatory treatment groups, compared with the no treatment group (Fig 4). There was no significant difference between the groups treated with cromolyn sodium and those treated with budesonide.

The number of hospitalizations for the whole group was significantly lower in the budesonide group compared with the control group but not significant for cromolyn. However, in a subgroup of atopic children, who had the most problems, the number of hospitalizations were equally reduced by both anti-inflammatory drugs. Thus, in this study, there was comparable efficacy at a very young age between cromolyn sodium and an inhaled corticosteroid.

In making the choice which anti-inflammatory drug should be used for early intervention, the risk-benefit ratio should be considered.

In terms of efficacy, head-to-head comparisons between cromolyn sodium and inhaled corticosteroids can be divided into 2 types of studies. In studies in which the patient population had severe asthma, the superiority of inhaled corticosteroids is obvious.²⁰⁻²² On the other hand, in studies where the children had mild-to-moderate asthma, 3²³⁻²⁵ of the 5 studies showed equal efficacy, while only 2 (1 of them an uncontrolled study) showed better results with inhaled corticosteroids.^{26,27} Thus in the patient with mild-to-moderate asthma, there is comparable efficacy.

As one moves towards patients with milder asthma, one should tolerate fewer side-effects. Both cromolyn sodium²⁸ and nedocromil sodium²⁹ have excellent safety records. The safety of inhaled corticosteroids, although very good,³⁰ is not as good as that of the nonsteroidal drugs.

Interestingly, the severity of the disease affects not only the efficacy but also the safety of inhaled cortico-

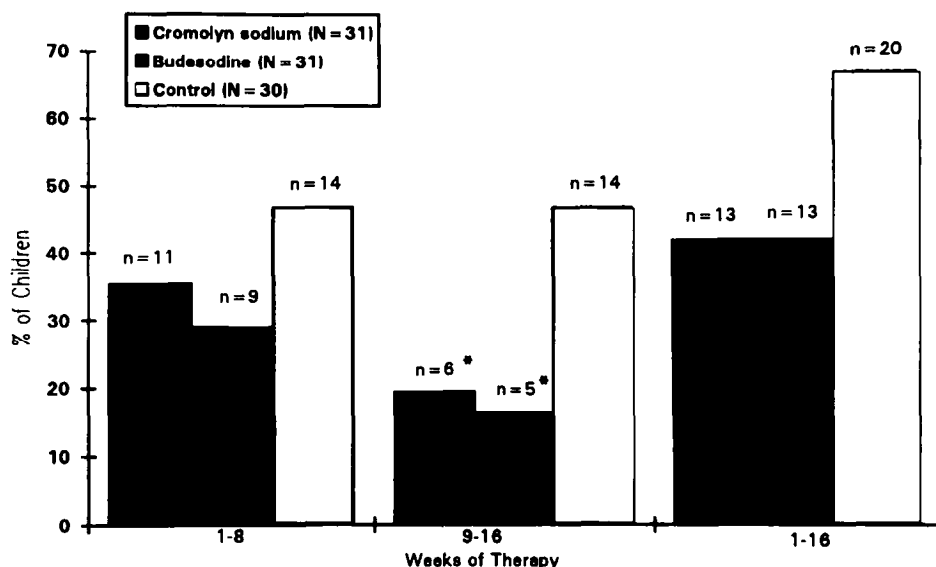


FIG 4. Children with at least 1 physician-diagnosed wheezing episode during anti-inflammatory therapy administered after bronchiolitis. For weeks 1 to 8, $P = .35$; weeks 9 to 16, $P = .01$; weeks 1 to 16, $P = .08$. Asterisks indicate that, in weeks 9 to 16, $P < .05$ compared with patients in the control group (χ^2 test). (From Reijonen T, Korppi M, Kuikka L, Remes K. Anti-inflammatory therapy reduces wheezing after bronchiolitis. *Arch Pediatr Adolesc Med* 1996;150:512-7. Copyright 1996, American Medical Association.)

steroids. Thus Harris and Fuller,³¹ treated adults with asthma with fluticasone propionate, which showed greater adrenal suppression in patients with milder asthma. It is possible, that in patients with more open airways, more of the drug penetrates and gets absorbed from the lungs, resulting in a greater systemic impact.

In children, the earlier studies with inhaled corticosteroids were performed on patients with severe asthma and found no growth suppression with regular doses (around 400 $\mu\text{g}/\text{day}$ of beclomethasone dipropionate).^{32,33} More recently, several studies in patients with mild-to-moderate³⁴ or mild³⁵ asthma showed significant growth suppression with beclomethasone dipropionate 400 $\mu\text{g}/\text{day}$.

As to why there would be more growth suppression in patients with milder asthma, the possible explanation is that, in patients with severe asthma, there is frequently a need for short or more prolonged courses of systemic corticosteroids, which have growth suppressive effect. The introduction of inhaled corticosteroids will eliminate or reduce the need for systemic corticosteroids. Poorly controlled asthma in itself causes growth suppression.³⁶ Treatment with inhaled corticosteroids will result in a great improvement in the control of asthma. Thus inhaled corticosteroids have 2 beneficial effects on growth, which balance out the negative effect and no growth suppression occurs. In patients with mild asthma, there is rarely any need for systemic corticosteroids, and the impact of inhaled corticosteroids on the control of asthma is not as dramatic as in patients with severe asthma. Thus the 2 beneficial effects on growth that were present in severe cases are absent or weaker, and the balance tilts toward growth suppression (Fig 5).

Weighing the pros and cons of how early pharmaco-

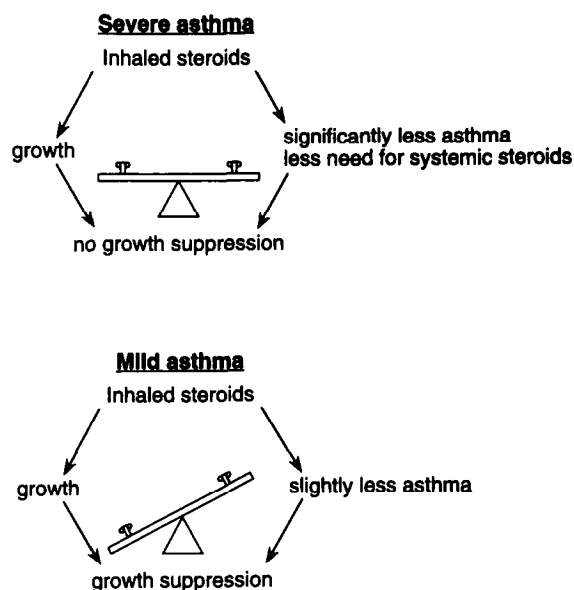


FIG 5. Growth suppression with inhaled corticosteroids in severe versus mild asthma. (From König P. Evidence for benefits of early intervention with non-steroidal drugs in asthma. *Pediatr Pulmonol* 1997;15(suppl):34-9. Copyright 1999. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

logic intervention (early after the onset of the disease or starting anti-inflammatory drugs in milder cases) should begin, several points need to be considered.

The main argument for starting early after the onset of disease was the hypothesis that, in the absence of inhaled steroid therapy, the course is progressively downhill, resulting in irreversible obstruction. This hypothesis has

now been refuted by several studies.¹¹⁻¹³ Treating all patients with asthma with inhaled anti-inflammatory drugs would be costly and difficult to implement or to justify, especially in today's trend toward managed care and cost containment. Obtaining good compliance with maintenance medication is difficult enough in patients with frequent symptoms. In those patients with infrequent symptoms (especially in the absence of data that this approach will have a definite beneficial effect on the long-term outcome), compliance would be extremely difficult.

To start anti-inflammatory treatment in milder cases than previously recommended,² a step-wise approach, is justified in 2 recent studies.^{11,12} The most recent set of international guidelines, the Global Initiative for Asthma,³⁷ recommended exactly this approach: to change the point of initiating inhaled anti-inflammatory treatment from patients symptomatic on more than 3 days per week² to patients symptomatic on more than 1 day per week.³⁷ This approach needs close clinical follow-up of patients with frequent measurements of pulmonary function tests to assess the severity of the disease and the changes in severity, which occur frequently in childhood asthma, both toward improvement (necessitating step-down in treatment) and sometimes toward worsening (necessitating step-up in therapy).

The decision whether steroidal or nonsteroidal drugs should be used for early intervention needs to take in consideration the following facts:

1. In mild-to-moderate asthma, inhaled nonsteroidal agents have comparable efficacy with the inhaled corticosteroids.²³⁻²⁵
2. Nonsteroidal drugs have a more favorable safety profile.^{28,29}
3. In addition to the known systemic and topical side effects of inhaled corticosteroids, there are several side-effects shown to occur in adults, but not studied in children, such as reduced skin collagen synthesis,³⁸ easy bruising and dermal thinning.³⁹⁻⁴¹
4. An increase in IgE synthesis has been shown in human subjects with systemic corticosteroids⁴² and with topical application of corticosteroids to the skin.⁴³ At the same time, there is evidence, at least in vitro, that both cromolyn sodium⁴⁴ and nedocromil sodium⁴⁵ inhibit IgE production.

In conclusion, the introduction of anti-inflammatory therapy in patients with milder asthma in a step-wise manner starting with inhaled nonsteroidal drugs is supported by studies,^{11,12} represents the recommendation of the latest guidelines,³⁷ and should now be the standard clinical practice.

Even though the hypothesis that without inhaled corticosteroids childhood asthma has a progressive downhill course is not supported by the latest data,^{11,12} it is possible that starting anti-inflammatory drugs early after the onset of the disease will result in even better long-term outcome than the approach of introducing these drugs in milder cases. This needs to be proved by prospective studies comparing the 2 approaches head-to-head.

Primary prophylaxis of asthma is an exciting possibil-

ity. Studies are needed to prove whether this can be achieved by treating with anti-inflammatory drugs early in life, before the occurrence of clinically manifest asthma, in children who are especially at risk to the development of persistent asthma, such as those children with a positive family history of asthma and an elevated IgE level in the first year.⁴⁶

REFERENCES

1. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88:373-81.
2. Warner JO, Götz M, Landau LI, Levison H, Milner AD, Pedersen S, et al. Management of asthma: a consensus statement. *Arch Dis Child* 1989;64:1065-79.
3. Hargreave FE, Dolovich J, Newhouse MT. The assessment and treatment of asthma: a conference report. *J Allergy Clin Immunol* 1990;85:1098-111.
4. National Heart, Lung, and Blood Institute, National Institutes of Health. International consensus report on diagnosis and management of asthma. Bethesda (MD): National Institutes of Health; 1992. Publication no. 92-3091.
5. Blair H. Natural history of childhood asthma. *Arch Dis Child* 1977;52:613-9.
6. Martin AJ, Landau LI, Phelan PD. Predicting the course of asthma in children. *Aust Paediatr J* 1982;18:84-7.
7. Kokkonen J, Linna O. The state of childhood asthma in young adulthood. *Eur Respir J* 1993;6:657-61.
8. Sears MR, Taylor DR, Print CG, Lake DC, Li Q, Flannery EM, et al. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990;336:1391-6.
9. Van Schayck CP, Dompeling E, van Herwaarden CL, Folgering H, Verbeek AL, van der Hoogen HJ, et al. Bronchodilator treatment in moderate asthma or chronic bronchitis: Continuous or on demand? A randomized controlled study. *Br Med J* 1991;303:1426-31.
10. Cockcroft DW, O'Byrne PM, Swystun V, Bhagat R. Regular use of inhaled albuterol and the allergen-induced late asthmatic response. *J Allergy Clin Immunol* 1995;96:44-9.
11. König P, Shaffer J. The effect of drug therapy on long-term outcome of childhood asthma: a possible preview of the international guidelines. *J Allergy Clin Immunol* 1996;98:1103-11.
12. Korppi M, Remes K. Asthma treatment in school children: lung function in different therapeutic groups. *Acta Paediatr* 1996;85:190-4.
13. Oswald H, Phelan PD, Lanigan A, Hibbert M, Carlin JB, Bowes G, et al. Childhood asthma and lung function in mid-adult life. *Pediatr Pulmonol* 1977;23:14-20.
14. Geller-Bernstein C, Levin S. Nebulized sodium cromoglycate in the treatment of wheezy bronchitis in infants and young children. *Respiration* 1982;43:294-8.
15. Furfaro S, Spier S, Drblik SP, Turgeon JP, Robert M. Efficacy of cromoglycate in persistently wheezing infants. *Arch Dis Child* 1994;71:331-4.
16. Henry RL, Hiller EJ, Milner AD, Hodges IGC, Stokes GM. Nebulized ipratropium bromide and sodium cromoglycate in the first two years of life. *Arch Dis Child* 1984;59:54-7.
17. Yüksel B, Greenough A. The effect of sodium cromoglycate on upper and lower respiratory symptoms in children born prematurely. *Eur J Pediatr* 1993;152:615-8.
18. Yüksel B, Greenough A. Inhaled nedocromil sodium in symptomatic young children born prematurely. *Respir Med* 1996;90:467-71.
19. Reijonen T, Korppi M, Kuikka L, Remes K. Anti-inflammatory therapy reduces wheezing after bronchiolitis. *Arch Pediatr Adolesc Med* 1996;150:512-7.
20. Francis RS, McEnery G. Disodium cromoglycate compared with beclomethasone dipropionate in juvenile asthma. *Clin Allergy* 1984;14:537-40.
21. Sarsfield JK, Sugden E. A comparative study of betamethasone valerate aerosol and sodium cromoglycate in children with severe asthma. *Practitioner* 1977;218:128-32.
22. Hiller EJ, Milner AD. Betamethasone 17 valerate aerosol and disodium cromoglycate in severe childhood asthma. *Br J Dis Chest* 1975;69:103-6.

23. Mitchell I, Paterson IC, Cameron SJ, Grant IWB. Treatment of childhood asthma with sodium cromoglycate and beclomethasone dipropionate aerosol singly and in combination. *Br Med J* 1976;2:457-8.
24. Shapiro GG, Sharpe M, DeRouen TA, Pierson WE, Furukawa CT, Virant FS, et al. Cromolyn versus triamcinolone acetonide for youngsters with moderate asthma. *J Allergy Clin Immunol* 1991;88:742-8.
25. Petersen W, Daugbjerg P, Fog E, Friis B, Howitz P, Pedersen FK, et al. Sodium cromoglycate (10 mg, tds) together with terbutaline (0.5 mg, tds) can replace inhaled steroids (200 mg) in childhood asthma [abstract]. *Eur Respir J* 1993;6(suppl II):356S.
26. Ng SH, Dash CH, Savage SJ. Betamethasone valerate compared with sodium cromoglycate in asthmatic children. *Postgrad Med J* 1977;53:315-20.
27. Price JF, Weller PH. Comparison of fluticasone propionate and sodium cromoglycate for the treatment of childhood asthma (an open parallel group study). *Respir Med* 1995;89:363-8.
28. König P, Shapiro GG. Cromolyn sodium: a review. *Pharmacotherapy* 1985;5:156-70.
29. Brogden RN, Sorkin EM. Nedocromil sodium: an updated review of its pharmacological properties and therapeutic efficacy in asthma. *Drugs* 1993;45:693-713.
30. Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. *Am Rev Respir Dis* 1993;148:S1-S26.
31. Harris TAJ, Fuller RW. High dose fluticasone propionate (FP) and its effect on serum cortisol (sCORT) in patients with asthma. *Eur Respir J* 1996;9(suppl 23):163S-4S.
32. Godfrey S, König P. Treatment of childhood asthma for 13 months and longer with beclomethasone dipropionate aerosol. *Arch Dis Child* 1974;49:591-6.
33. Allen DB, Mullen M, Mullen B. A meta-analysis of the effect of oral and inhaled corticosteroids on growth. *J Allergy Clin Immunol* 1994;93:967-76.
34. Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderately severe asthma in children. *Pediatrics* 1993;92:64-77.
35. Doull IJM, Freezer MJ, Holgate ST. Growth of prepubertal children with mild asthma treated with inhaled beclomethasone dipropionate. *Am J Respir Crit Care Med* 1995;151:1715-9.
36. Ninan TK, Russell G. Asthma, inhaled corticosteroid treatment, and growth. *Arch Dis Child* 1992;67:703-5.
37. Global initiative for asthma: Global strategy for asthma management and prevention NHLB/WHO workshop report. Bethesda (MD): National Institutes of Health; 1995. Publication No. 95-3659.
38. Autio P, Karjalainen J, Risteli L, Risteli J, Kiistala U, Oikarinen A. Effects of an inhaled steroid (budesonide) on skin collagen synthesis of asthma patients *In Vivo*. *Am J Respir Crit Care Med* 1996;153:1172-5.
39. Capewell S, Reynolds S, Shuttleworth D, Edwards C, Finlay AY. Purpura and dermal thinning associated with high dose inhaled corticosteroids. *Br Med J* 1990;300:1548-51.
40. Mak VHF, Melchor R, Spiro SG. Easy bruising as a side-effect of inhaled corticosteroids. *Eur Respir J* 1992;5:1068-74.
41. Roy A, Leblanc C, Paquette L, Ghezzi H, Côté J, Cartier A, et al. Skin bruising in asthmatic subjects treated with high doses of inhaled steroids: frequency and association with adrenal function. *Eur Respir J* 1996;9:226-31.
42. Zieg G, Lack G, Harbeck RJ, Gelfand EW, Leung DYM. In vivo effects of glucocorticoids on IgE production. *J Allergy Clin Immunol* 1994;94:222-30.
43. Hiratsuka S, Yoshida A, Ishioka C, Kimata H. Enhancement of in vitro spontaneous IgE production by topical steroids in patients with atopic dermatitis. *J Allergy Clin Immunol* 1996;98:107-13.
44. Kimata H, Yoshida A, Ishioka C, Mikawa H. Disodium cromoglycate (DSCG) selectively inhibits IgE production and enhances IgG4 production by human B cells in vitro. *Clin Exp Immunol* 1992;84:395-9.
45. Loh RKS, Jabara HH, Geha RS. Mechanisms of inhibition of IgE synthesis by nedocromil sodium: nedocromil sodium inhibits deletional switch recombination in human B cells. *J Allergy Clin Immunol* 1996;97:1141-50.
46. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, et al. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133-8.

47. Diaz P, Galleguillos FR, Gonzalez MC, et al. Bronchoalveolar lavage in asthma: the effect of disodium cromoglycate (cromolyn) on leukocyte counts, immunoglobulins and complement. *J Allergy Clin Immunol* 1984;74:41-8.
48. Manolitsas ND, Wang JH, Devalia JL, Trigg CJ, McAulay AE, Davies RJ. Regular albuterol, nedocromil sodium and bronchial inflammation in asthma. *Am J Respir Crit Care Med* 1995;151:1925-30.
49. Tinkelman DG, Reed CE, Nelson HS, Offord KP. Aerosol beclomethasone dipropionate compared with theophylline as primary treatment of chronic, mild to moderate severe asthma in children. *Pediatrics* 1993;92:64-77.

DISCUSSION

O'Connor: First, could you define an anti-inflammatory drug? Second, do we have evidence that either chromones or inhaled steroids alter inflammation as measured by bronchoalveolar lavage, sputum, or bronchial biopsy? Third, why do chromones work in mild-to-moderate but not severe asthma?

P. König: My personal definition of an anti-inflammatory drug is one that reduces bronchial hyperreactivity and inflammation in humans, as shown by bronchoalveolar lavage or biopsy. Diaz et al⁴⁷ have shown that cromolyn sodium reduces eosinophils in bronchoalveolar lavage. With nedocromil sodium the only evidence⁴⁸ at this time is that, compared with maintenance adrenergic therapy, nedocromil sodium is significantly better. Mild asthma could well have a different pathogenesis than severe asthma. There are numerous studies that show the efficacy of nedocromil sodium in severe, steroid-dependent asthma. There is no such evidence with cromolyn sodium.

Costello: When you talk about suppression of growth, are you talking about growth velocity or about final height? Also, in the study by Tinkelman et al,⁴⁹ only the growth of boys was affected by inhaled corticosteroids. Is there a general view that boys are more susceptible to growth inhibition?

P. König: There is some hint that boys may be more susceptible but no solid evidence. The studies showed that growth velocity was reduced by inhaled corticosteroids in mild-to-moderate, but not severe, asthma. Data published to date on final height attained showed no effect from inhaled steroids, but those studies are in patients with severe asthma. The use of inhaled steroids in patients with milder asthma is a relatively recent development, and the long-term effect is not known.

C. Page: In the study by Tinkelman et al,⁴⁹ theophylline was compared with inhaled beclomethasone and produced comparable efficacy. There is now increasing evidence that sub-bronchodilator levels of theophylline have anti-inflammatory actions in patients with asthma. It is orally active and inexpensive, having fewer side effects at the lower plasma levels. What is your view on the place of theophylline in the treatment of pediatric asthma?

P. König: In view of the systemic side-effects and the lack of evidence on reduced bronchial hyperreactivity and reduced inflammation by bronchoalveolar lavage or biopsy, I think that theophylline should be used only as an additional treatment to cromolyn sodium or with nedocromil sodium or inhaled corticosteroids in difficult to treat cases.