

## The Management of Asthma in the '90s

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### Curriculum vitae

Dr D Danilewitz graduated MBChB from UCT in 1954 and after 3 years in hospital practice, entered general practice in Klerksdorp where he remained for 22 years. In 1980 Dr Danilewitz joined Fisons as their medical director, a post he still holds. For the past 9 years Dr Danilewitz has worked at the asthma clinics of the J. G. Strydom and Johannesburg hospitals. Dr Danilewitz's main interests are allergy, asthma and continuing medical education.

### Summary

*Bronchial asthma is increasing in prevalence, severity and mortality. The GP should take time to explain fully to his patient the nature of his disease, the objectives of the treatment, and the meaning of good control. Recent advances in pharmacological management are evaluated and a few relevant studies explained.*

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### KEYWORDS:

Asthma; Drug Therapy; Patient Education; Physician-Patient Relations

### Introduction

Bronchial asthma is the commonest disease affecting the respiratory tract in man, affecting all ages: from the very young to the elderly. In spite of all the advances in the pharmacological management of such a widespread chronic disease, asthma patients are no better off today than they were 20 years ago, and in fact asthma is the only common treatable condition that is increasing in prevalence, severity and mortality.

The diagnosis and management of asthma are straightforward, and yet this disease remains underdiagnosed and good treatment is still being denied to many patients.<sup>1</sup> Is this an indication of inadequate treatment? Or is good treatment not being used optimally?

### Pathogenesis

Our understanding of the pathogenesis of asthma has changed

dramatically in the last 10 years with the recognition that disordered airway function may be linked to airway inflammation.

The results of a study recently conducted by Beasley and Holgate<sup>2</sup> in Southampton, showed that inflammatory changes similar to those seen in subjects who had died from a severe attack of asthma, were observed in subjects who would clinically be considered to have mild stable asthma. These observations suggest that pharmacological treatment directed against the underlying inflammatory processes in asthma, should not be limited to those patients with severe forms of the disease. The treatment of asthma should therefore be primarily directed towards controlling the airway inflammation while at the same time trying to promote bronchodilatation.

### Management

The main objective of treatment should be to reduce symptoms to a minimum and to improve lung function to a maximum. This can be achieved by avoidance strategies, medications and patient education.

### Avoidance Strategies

Every asthmatic should try to identify the trigger mechanisms contributing to exacerbations of their asthma and then, once identified, to either avoid them or else use prophylactic medications pre-emptively. When identified and avoidance is impossible, then prophylactic use of sodium cromoglycate inhaled corticosteroids or Nedocromil Sodium is advised.

Avoidance strategies are of great

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importance in occupational asthma and where a chemical sensitizer is identified, then avoidance, protective masks or prophylactic drugs should be used.

The role of foods<sup>3,4</sup> in precipitating asthma, is uncertain but appears to be uncommon. However, nuts, strawberries and shellfish have been implicated in adults while milk, wheat, eggs and mealies have been implicated in children.

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Asthma patients are no better off today than 20 years ago

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The same applies to food additives such as monosodium glutamate or metabisulphite used as a preservative in salads, wine, beer, fruit juices and dried fruit.

### Medication

The objectives in the pharmacological management of asthma are:

1. Treat the underlying inflammation
2. Reverse bronchoconstriction
3. Avoid side-effects

### Anti-inflammatory drugs used in asthma

Three main drugs in this category will be discussed:

1. Sodium Cromoglycate
2. Corticosteroids
3. Nedocromil Sodium

### *Sodium Cromoglycate*

Sodium cromoglycate is a derivative of chromone-2-carboxylic acid which is given by inhalation for the treatment of asthma.

### *Mode of Action*

Despite intensive research, a precise mechanism of action is still not known. Although sodium cromoglycate is classically known for its mast cell stabilization, new information suggests it has an effect on other inflammatory cells such as macrophages and eosinophils.

This accounts for its ability to inhibit not only the immediate response to allergen and exercise, but also the late response and the subsequent bronchial hyperresponsiveness, which is one of the hallmarks of asthma.

A further proposed mechanism of action is that sodium cromoglycate may inhibit neuronal reflexes within the lung, which may explain why sodium cromoglycate reduces the symptoms of asthma (particularly coughing) in patients so effectively.

### Clinical Use

The primary indication for sodium cromoglycate is for the treatment of mild to moderate asthma and clinical trials have shown that 60-80% of patients can be adequately controlled on sodium cromoglycate as first-line therapy.

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Asthma is the only treatable condition that is increasing in prevalence, severity and mortality

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The time has now come to put to rest the misconception that sodium cromoglycate is only for children, as even adults with late onset non-allergic asthma may benefit from its

use. It is now generally accepted that sodium cromoglycate is the anti-inflammatory drug of first choice in childhood asthmatics. This was confirmed by an international panel of respiratory paediatricians in London<sup>5</sup> in December 1988 and endorsed by the South African Childhood Asthma Working Group<sup>6</sup> consensus meeting in November 1989.

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Reduce symptoms to the minimum, and improve lung function to the maximum

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Thus children using intermittent bronchodilators and remaining symptomatic should have sodium cromoglycate added to their treatment regimen.

It is also a misconception that sodium cromoglycate should be stopped during acute exacerbations and especially if nebulization with a beta two agonist is being used, sodium cromoglycate can be added to the nebulizing solution.

Side effects with sodium cromoglycate are minimal and the only minor side effect reported is throat irritation, when the powder is inhaled.

### *Corticosteroids*

The basis of use of corticosteroids in asthma is their potent anti-inflammatory action. The serious side effects of systemic steroids stimulated the development of the inhaled forms such as beclomethasone dipropionate and Budesonide.

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*Mode of Action*

It is believed that steroids stimulate the production of lipocortin which inhibits the production of phospholipase A<sub>2</sub>, leading to a reduction in the synthesis of prostaglandins, leukotrienes and platelet activating factor.

The effect of this is to inhibit release of mediators from macrophages and eosinophils which leads to inhibition of the late phase of asthma, which is the inflammatory phase.

Another important effect of corticosteroids is their prevention and reversal of down-regulation of pulmonary beta adrenergic receptors and in this way, prevents the development of tolerance during longterm therapy with beta adrenergic agents.

*Clinical Use*

Inhaled corticosteroids are effective in all types of asthma in both children and adults. In children its use should be reserved for those cases not responding to sodium cromoglycate.

### Disordered airway function may be linked to airway inflammation

The clinical response to inhaled steroids is dose-related and some patients will respond to as little as 400 UG daily, whereas others require doses up to 2 000 UG daily. The introduction of high-dose steroid inhalers has been of great value in steroid dependant asthmatics where it is often possible to reduce the dose of oral steroids.

In a minority of patients, not well controlled on even high dose inhaled steroids, it is necessary to use oral steroids. When necessary, oral steroids should be administered first thing in the morning and in some patients, it may be possible to control their asthma by alternate morning dosing.

Oral steroids are of great value in controlling the acute exacerbations of asthma when short courses of high

### Good treatment is still being denied to many patients

dose steroids are given in doses of 30 to 60 mg in a single dose every morning for 10 to 14 days. Higher doses may be necessary in patients already maintained on oral steroids.

Where short courses of high dose steroids are given for acute exacerbations, it is not necessary to taper the treatment. Another indication for short term high dose steroids is in patients where you wish to demonstrate maximum reversibility and also in patients where there is a question of reversibility being present eg in chronic bronchitis.

*Side Effects*

Inhaled corticosteroids are usually well tolerated. Oral thrush occurs in adults and to a lesser extent in children.<sup>7</sup> Dysphonia is less commonly seen. In adults, suppression of the adrenal glands may occur with doses of beclomethasone dipropionate above 1500 UG whereas in children adrenal suppression has been reported with doses as low as 400 UG daily.<sup>8</sup>

*Nedocromil Sodium*

Nedocromil sodium is the sodium salt of a pyranoquinoline dicarboxylic acid and is a new bronchial anti-inflammatory agent which has been shown to be effective as a first-line maintenance therapy in asthma in adult patients. Regular use of this non-steroidal therapy by inhalation, has been shown to achieve significant reduction in the frequency and severity of symptoms, whether or not the condition is of allergic etiology. Nedocromil sodium exerts specific inhibitory effects on a wide range of inflammatory cells which contribute to all phases of the inflammatory state in the airways. In clinical pharmacology, nedocromil sodium has been shown to inhibit both the immediate and late phase reactions and prevent increases in bronchial hyperresponsiveness, which is so critical in asthma.

Clinically, nedocromil sodium has been shown to be effective in the management of a wide range of patients regardless of etiology. The twice daily dosage regime will give convenient control of symptoms for many patients,

### The role of foods is still uncertain

however, severe symptoms may necessitate the use of nedocromil sodium four times daily until control is established and then reduced to twice daily.

Nedocromil sodium has also been shown to be compatible with all other therapies and may permit the full or partial reduction of existing maintenance therapy, such as

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theophyllines, inhaled B2 agonists and low dosage inhaled corticosteroids.

Nedocromil sodium is indicated as a first line treatment in adult asthmatics and should be started as soon as the diagnosis of asthma is made except in patients presenting with acute severe asthma who first need to be brought under control and when stabilised, put onto nedocromil sodium.

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Bronchodilators are today regarded more as agents used in acute asthma, and as rescue therapy in chronic asthma

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Nedocromil sodium is also indicated in patients on regular round-the-clock bronchodilators and who are still symptomatic and thirdly as an add-on therapy in patients not well controlled on existing therapy such as B2 agonists, theophyllines and inhaled steroids.

Nedocromil sodium is also effective in exercise induced asthma. Side effects with nedocromil sodium are minimal and consist mainly of headache, nausea and some patients have reported a bitter taste.

### Bronchodilators

For many years regarded as the mainstay of asthma treatment, the bronchodilators are today regarded mostly as agents to be used in acute asthma and as rescue therapy in chronic asthma. Bronchodilators have no effect on airway inflammation and overreliance on them masks the underlying pathology.

### *Beta Two Adrenergic Agonists*

The more selective inhaled B2 agonists are today regarded as the most effective and safest bronchodilators available.

Their mechanism of action is by increasing intracellular cyclic amp in airway smooth muscle. These agents relax the smooth muscle of all airways irrespective of the bronchoconstricting challenge. B2 agonists act within minutes and their effect lasts for 3 to 6 hours. Very little difference exists between the various B2 agonists available.

Clinically important tolerance very rarely develops and if patients complain that their B2 agonists are no longer effective, it is an important indication of deteriorating asthma and it will not help to change the inhaler. Another important indication of worsening asthma is more frequent use of these inhalers.

B2 agonists by inhalation are very effective in the prevention and relief of exercise induced asthma.

The main drawback of the presently available B2 agonists, are their

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**Bronchodilators have no effect on airway inflammation and may even mask the underlying pathology**

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relatively short duration of action. Oral B2 agonists are best reserved for those patients (infants, children and elderly) who cannot be taught to use an aerosol inhaler.

### *Side-Effects*

Tremor, tachycardia and palpitations are the commonest side-effects and occur mostly when B2 agonists are taken orally or by nebulization.

### *Theophylline*

The use of theophylline as a bronchodilator, has diminished over the past few years. This is mainly due to its side-effects, especially in children and the fact that it is less effective as a bronchodilator than the B2 agonists.

The mechanisms of action of theophylline has never been fully

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**Poor compliance is probably the most common cause of failure**

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elucidated and over the past 50 years, different hypothesis have been postulated varying from phosphodiesterase inhibition to antagonism of adenosine receptors to inhibition of intracellular release of calcium.

Also controversial is whether the theophyllines have any anti-inflammatory effect on the asthmatic airways. Against this effect is the fact that long-term administration does not reduce bronchial hyperresponsiveness.

Nevertheless, theophyllines are still extensively used and have an important role to play especially in preventing nocturnal asthma and as a bronchodilator in patients unable to use an aerosol inhaler.

The main drawback with the use of

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theophylline is the high incidence of side-effects such as nausea, vomiting, headache and more seriously, cardiac arrhythmias and seizures.

Recently evidence of learning difficulties in children<sup>9</sup> with asthma receiving long-term theophylline therapy has been demonstrated. Another drawback of theophylline usage, is the fluctuations in plasma concentrations that occur with use of various drugs and conditions such as acute viral conditions, cardiac failure and hepatic disease. In these circumstances, the plasma levels of theophylline must be monitored.

### Anticholinergic Agents

Ipratropium bromide, the only anticholinergic agent available, acts by blocking muscarinic receptors in airway smooth muscle and thus inhibits cholinergic tone resulting in bronchodilatation. Although ipratropium bromide has a longer duration of action than B<sub>2</sub> agonists (six to eight hours), it has a delayed onset of action (thirty to sixty minutes).

### Patients' ignorance reflects poor doctor-patient communication

Perhaps its greatest role is an additive agent with B<sub>2</sub> agonists because when used together, a greater degree of bronchodilation and longer duration of action has been observed than when B<sub>2</sub> agonists are used alone.

This is especially true when ipratropium bromide is added to a B<sub>2</sub> agonist for nebulization.

### Side-Effects

These are very uncommon and consist of mild pharyngeal irritation, dry mouth or bitter taste.

### Patient Education

Poor compliance is probably the most common cause of failure of treatment in asthma and one of its main contributing factors is the lack of communication between the doctor and patient. Patients' ignorance about their disease largely reflects this poor communication.

Studies have repeatedly shown that asthmatics have little knowledge of their disease and the objectives of its management. This has led to

### Patients should get *written* instruction

underestimation of their condition and consequent failure to adequately respond to acute exacerbations.

A report in the BMJ by Bucknall<sup>10</sup> et al, reported that two thirds of their patients had no idea how their treatment worked, 87% could not recall advice about oral steroids and a third could give no plan to cope with an acute attack. Even during fatal attacks the British Thoracic Association<sup>11</sup> found that two thirds of both patients and general practitioners failed to appreciate the severity of asthma.

It is therefore imperative that every asthmatic should have the nature of his disease explained to him, the objectives of treatment with a simple explanation of the mode of action of

his medication and also the meaning of good control. Initial treatment of the patient to determine the least symptoms and the best FEV<sub>1</sub>, or PEF<sub>R</sub>, allows both the patient and

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66% had no idea how their treatment worked 87% could not recall advice about oral steroids 33% could give no plan on how to cope with an acute attack?

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his doctor appreciate the degree of control that is possible. If there is any doubt about this, a trial of anti-inflammatory treatment such as sodium cromoglycate, nedocromil sodium, inhaled or oral corticosteroids, should be given to try and establish the best control for each patient.

Patients should be given written instructions on how to increase their anti-inflammatory medications when their asthma worsens and also how to recognize and respond to acute exacerbations. In this latter regard, patients should be given supplies of oral corticosteroids (preferably prednisone or prednisolone) and instructed in writing, how to use them in emergency. Patients must also know when to phone the doctor for advice.

Crucial in the self management of the more troublesome asthmatic, is for them to have their own Wright peak flow meter and to be instructed on the importance of recognizing wide diurnal variations. A level of 10 to 20% variation in peak flow readings

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between morning and night correlates with mild symptoms of asthma, 20 to 30% moderate symptoms and greater than 30% severe symptoms.

Similarly asthmatic children (or their parents) should be taught to increase their asthma therapy at the first sign

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**The commonest precipitating factor is viral infection: increase therapy at the very first sign!**

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of a viral infection, as this is the commonest precipitating factor of acute severe asthma in childhood.<sup>12</sup>

### Conclusions

The successful management of the patient with asthma demands not only the judicious prescribing of the correct medication, but also the education of the patient. This should be regarded as the cornerstone of treatment and time must be spent discussing and explaining all aspects of their disease with them. This is the only way in which we can ever hope to reduce the mortality and morbidity of this common condition.

There are few more satisfying experiences in the practice of medicine than the relief and gratitude of an asthmatic that you have helped. With the availability today of all the excellent medications, and with just a few moments of time, this experience is within the reach of all family practitioners.

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