Prophylactic inhalation therapy in preschool children with asthma

The main studies of this thesis were funded by a grant from the Netherlands Asthma Foundation. The Netherlands Asthma Foudantion also supported the publication of this thesis.

Cover illustrations: Goof, Wietske en Thijs van der Kamp
Cover design: Iris de Jong
Layout: Bon Mot, Rotterdam
Printing: Drukkerij Elinkwijk BV, Utrecht

ISBN 90-74494-09-9

Prophylactic inhalation therapy in preschool children with asthma

Profylactische inhalatietherapie voor jonge kinderen met astma

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof.dr P.W.C. Akkermans M.A.
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 24 februari 1999 om 15:45 uur

door

Maria Johanna Aleida Tasche

geboren te Hengelo (O).

Promotiecommissie

Promotores	:	Prof.dr J.C. de Jongste Prof.dr S. Thomas
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In loving memory of my father

Dedicated to my mother

Publications and manuscripts related to the studies described in this thesis

Tasche MJA, Uijen JHJM, Ponsioen BP, van Suijlekom-Smit LWA, de Jongste JC, van der Wouden JC. Preschool children with asthma: are they known to their GP? [in press]

Tasche MJA, van der Wouden JC, Uijen JHJM, Ponsioen BP, Bernsen RMD, van Suijlekom-Smit LWA, de Jongste JC. Randomised placebo-controlled trial of inhaled sodium cromoglycate in 1-4 year old children with moderate asthma. Lancet 1997; 350: 1060-4

Tasche MJA, van der Wouden JC, Uijen JHJM, Ponsioen BP, Bernsen RMD, van Suijlekom-Smit LWA, de Jongste JC. Inhalatie therapie met cromoglicaat by kleine kinderen met matig ernstig astma. Huisarts Wet 1998; 5: 229-35

Tasche MJA. Author's reply on comments. Lancet 1998; 351: 369

Tasche MJA, de Jongste JC. Inhalatie van cromoglicinezuur via een voorzetkamer: geen effect op de symptomen van peuters met matig ernstig astma. Ned Tijdschr Geneeskd 1998; 142: 828-9

Tasche MJA, de Jongste JC. Re: Inhalatie van cromoglicinezuur via een voorzetkamer: geen effect op de symptomen van peuters met matig ernstig astma. Ned Tijdschr Geneeskd 1998; 142:2061-2

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Tasche MJA, Bernsen RMD, Uijen JHJM, Ponsioen BP, van Suijlekom-Smit LWA, van der Wouden JC, de Jongste JC. Feasibility of long-term inhalation therapy in preschool children with moderate asthma. [submitted]

Tasche MJA, Bernsen RMD, van der Wouden JC, van Suijlekom-Smit LWA, Ponsioen BP, Thomas S, de Jongste JC. Adhesion to long-term asthma prophylaxis in preschool children. [submitted]

Tasche MJA, Uijen JHJM, Bernsen RMD, de Jongste JC, van der Wouden JC. Inhaled sodium cromoglycate in children with asthma: a systematic review. [submitted]

Tasche MJA, Brinkhorst G, Vulto AG. Inhalatietherapie bij kinderen: welke toedieningsvorm? Pharm Weekbl 1998; 133:428-32

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contents

General introduction

Respiratory diseases are a major cause of morbidity in preschool children. Confronted with young children with respiratory symptoms *the physician* faces many uncertainties regarding the diagnosis, treatment and prognosis, namely:

- labelling of chronic and recurrent respiratory symptoms and defining 'asthma';
- the natural course of respiratory symptoms and the relation with future asthma;
- the effectivity and side-effects of anti-asthma treatment, for both relief and prophylaxis;
- the feasibility of and compliance with prophylactic inhalation therapy.

In studying effectivity of anti-asthma drugs, *the investigator* has additional problems:

- symptoms as outcome measure;
- the difficulty of conducting clinical trials, finding the appropriate setting and considering the ethical aspects of research in young children.

In this chapter, the background of these uncertainties for physicians and investigators will be explored further. The place of sodium cromoglycate in prophylactic therapy will be discussed in detail because it is the main focus of the studies in this thesis. The results of this research will be presented in the following chapters together with results of studies on preschool asthma in general practice and on the feasibility of and adherence to maintenance inhalation therapy.

Labelling chronic and recurrent respiratory symptoms in young children

Presentation of asthma symptoms in young children varies from acute wheezy episodes, often associated with viral infections, to recurrent daily symptoms. These symptoms can be labelled in different ways; i.e. asthma, recurrent or persistent wheezing. These terms are ill defined1 since a suitable method of lung function measurement to distinguish between the diagnoses is lacking. The debate on the term "asthma" is ongoing: without qualification or definition the term is too imprecise.[2] Data reporting the prevalence of 'asthma' and 'wheezing' in children under the age of four years to range between 10% and 20% [3,4], have to be considered in this perspective; the variation could be the result of different definitions. It has been suggested to use the term "asthma" for children with measurable reversible airway obstruction, but this raises difficulties for preschool children in whom even measurement of peak flow is not possible and findings of physical examination are not precise. In this age group we considered that the diagnosis of asthma should be applied to children whose symptoms and burden of disease warrant specific treatment. This means that, in our studies, the separate terms 'asthma' and 'wheezing' are combined under the label 'asthma'. In this

line of thought, a positive response to a therapeutic trial of a β_2-agonist and/or inhaled steroid therapy may help to identify the disease,[5] whereby this judgement is solely based on subjectively measured symptom relief.

Natural course of respiratory symptoms related to future asthma

It is known that some of the children with symptoms suggestive of asthma under the age of four years will have asthma in the future, because most of them outgrow the symptoms.[6-8] So far, it has not been possible to detect with any certainty the individual prognosis of asthmatic infants with recurrent wheeze. The prime limiting factor in measuring outcome is the inability to verify the disorder itself in an objective manner.[4] There is evidence that acute viral wheezy episodes in the very young represent a type of airway disease clinically distinct from atopic asthma.[6,7,9] Martinez and colleagues measured lung function by the chest compression technique in 125 one-year-olds and showed that lung function before the first wheezy episode may predict wheeze during the first 2-3 years but not at six years of age.[6] They defined two types of wheezing infants: a group with transient wheeze associated with diminished airway function at birth and not having increased risks of asthma or allergies in later life, and another type with wheezing episodes related to a predisposition to asthma. It is not clear, however, how these two types of children can be distinguished by different clinical patterns prospectively, and whether or not they require different therapeutic approaches, such as relief therapy on demand or anti-inflammatory prophylaxis.

Effectivity of prophylactic anti-asthma treatment

The possible existence of different types of wheeze in young children, requiring different therapies, may explain the variable findings in trials with asthma medication in preschool children.[10-12]

Until the revision of the British Thoracic Society guidelines for asthma in 1997, inhalation therapy with sodium cromoglycate was recommended as first-choice prophylactic treatment for moderate asthma in young children.[5,13] From 1997 inhaled steroids and sodium cromoglycate occupied an equal place in the recommendations.[5] The most recent guidelines state that the balance of risk and benefit may be negative for treatment of mild cases with inhaled steroids, because of the unknown long-term side-effects in early childhood. For such children, cromoglycate should still be considered as first-choice preventive treatment. Recent United States guidelines continue to recommend cromoglycate as first choice in infants and young children[14]; this despite the fact that data on the

effectivity of sodium cromoglycate in preschool children with mild and moderate asthma is lacking.

Sodium cromoglycate

Roger Altounyan was born in 1922 and he was first diagnosed with allergic asthma when he was a medical student.[15] He noted that one compound derived from khellin, a plant extract, appeared to decrease the antigen response in sensitised guinea pig tissue. This observation convinced him that it would be possible to develop a drug that treated asthma by blocking the release of mast cell mediators rather than by simply antagonising their effects. Between 1957 and 1964 he tested various compounds on himself for their anti-allergic properties. After testing hundreds of derivatives of khellin he identified one compound, disodium cromoglycate, that was consistently able to attenuate his allergic response.[16] In a first paper (1964) a patient, Altounyan himself, had a fall in FEV_1 after antigen challenge, and inhaled cromoglycate provided significant protection.[17] The next step was a clinical trial conducted by his friend Dr Jack Howell.[18] A group of 10 adults was studied using a double-blind, crossover design. There was a two-week run-in period and two weeks of placebo, preceded or followed by two weeks of nebulised cromoglycate. The outcome variable was the clinical judgement by Howell and he judged that all 10 subjects were better during the treatment period with the active drug than with placebo. Many trials have since been undertaken, and the overall conclusion was that inhaled SCG is an effective treatment in 70% of asthmatic patients. In the history of cromoglycate two important trials were published in 1972: in school-age children[19] and in adults.[20] Cromoglycate became a major therapeutic agent in the treatment of asthma and Altounyan is still honoured by an annual lecture for his discovery.

Sodium cromoglycate was first introduced as an inhaled treatment for bronchial asthma in the late 1960s. Initially it was presented as 20 mg sodium cromoglycate combined with 0.1 mg isoprenaline sulphate in a capsule which was inhaled using a spinhaler. Shortly afterwards cromoglycate without isoprenaline was introduced and newer formulations were manufactured; e.g. an aqueous solution for nebulisation and metered dose inhalers. The most commonly used form at present is the metered dose inhaler delivering 5 mg cromoglycate per actuation.
In addition to the effect on mast cells, sodium cromoglycate has inhibitory actions on macrophages, eosinophils, monocytes and platelets, all important components in the inflammatory response of asthma. Its mechanism of action is not yet fully understood.[21] Cromoglycate has no acute bronchodilator effect and must be used continuously to control asthma inflammation in a prophylactic way. In addition to long-term prophylaxis, cromoglycate can be used as a prophylactic immediately before exposure to bronchoconstricting stimuli, like exercise.[22]

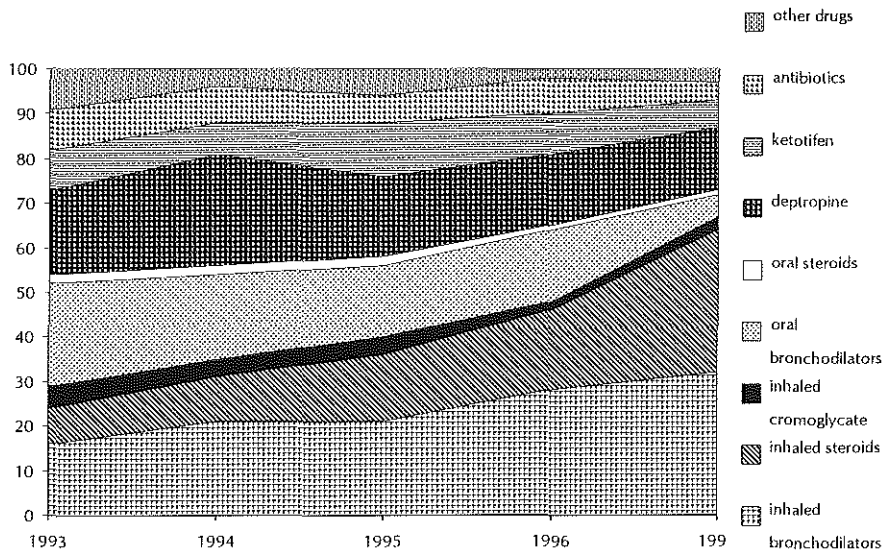

Figure 1
Distribution of asthma prescriptions in 1-4-year old children in general practice

Recent trends in anti-asthma drug prescriptions

Already before the change in guidelines inhaled steroids became more important and are regarded today as first-line prophylactic anti-inflammatory treatment.[5,23] There is also a trend in favour of using inhaled steroids in mild asthma in children, presumably due to their higher potency.[23] In the UK 52%, of 17000 children with asthma from 398 general practices were prescribed preventive treatments in 1990[24]; 17% were prescribed cromoglycate (a declining number) and 39% inhaled steroids (a rising number). In a survey by Anderson and colleagues that reported the use of anti-asthmatic drugs in 1978 and 1991, the proportion of wheezy children increased from 26% to 57%.[25] The use of inhaled steroids had increased from 2% to 17%, but changes in the use of cromoglycate were not specified. In the Netherlands the number of prescriptions for cromoglycate has decreased during the 1990s, both from general practitioners and specialists, and the number of consultations for 'asthma' has increased.[26] Figure 1 shows the distribution of drugs prescribed for asthma in children 1-4 years, by Dutch general practitioners in 1993-1997.[26]

A notable finding is the decline in the number of prescriptions for sodium cromoglycate at a time when the drug was still recommended as first choice prophylactic treatment in children with moderate asthma, both in the UK[5,24] and in

the Netherlands[27] and when the risk of overtreatment with inhaled steroids in young children with mild asthma had been noticed.[28-30] The issues of the efficacy and safety of long-term steroid treatment in preschool children are still unsolved due to insufficient knowledge on the optimal dose, lung deposition and delivery from the available devices.[29] Moreover, the majority of studies evaluating the risk of systemic side-effects have addressed children older than five years. A potential role for sodium cromoglycate in the treatment of moderate asthma in young children still exists. A retrospective study even suggested that cromoglycate may improve the long-term prognosis of childhood asthma.[31]

Achieving control of asthma in young children remains difficult, as reflected by increasing morbidity on the one hand, and the increasing use of anti-inflammatory therapies on the other.[3,24,32,33] This, and the uncertainties about the effectiveness of sodium cromoglycate and about long-term side-effects of inhaled steroids, prompted us to investigate and review the effects of sodium cromoglycate in young children with asthma.

Feasibility of and compliance with inhalation therapy

Inhalation therapy is the preferable way to administer anti-asthma medication to children,[5] because it enables the drug to act directly and selectively. The availability of spacer devices with facemasks has extended the applicability of metered dose inhalers to preschool children and their use is more simple than the use of nebulizers. Spacer devices and nebulizers have shown to be equally effective.[34,35] Various spacer devices with facemasks are available for symptomatic and prophylactic treatment. Little is known, however, about the feasibility in terms of parent/patient adherence and compliance in children aged 1-4 years in the home situation. Compliance with inhaled asthma treatment in children and adults is generally poor. The extent to which asthma patients of all ages follow prescribed treatment plans is reported to range from 30% to 70%.[36] Non-adherence may have considerable consequences for morbidity, clinical trial outcomes and costs of treatment.

Conducting clinical trials in an appropriate setting

Clinical trials of effectivity of asthma drugs are complicated in young children, mainly because of the uncertainties mentioned previously and because of the ethical aspects of research in this age group. In the Netherlands, most children with asthma are treated by their general practitioner.[26,37] Only complicated cases

or children with severe asthma are referred to and treated by a specialist. Since sodium cromoglycate is recommended for children with moderate asthma, the most appropriate setting to investigate the effectivity of cromoglycate is in the home situation, with children enrolled from general practices. The biggest challenge of conducting a randomised controlled trial in general practice is the enrolment of participating physicians and patients.[2,5,7] Being mainly a data collector, the general practitioner may be daunted by time-consuming and tedious extra work of instructing the patients, registering baseline and follow-up data, etc. Therefore, trials in general practice are at risk of failure due to unsuccessful data collection and require specific methodology.

Symptoms as outcome measure

This item is closely related to the difficulty of diagnosing asthma in young children. Again, the most important limiting factor in measuring outcome is the inability to measure asthma itself.[1] In young children, symptom assessment is the basis for most clinical treatment schemes, although symptoms are poorly defined and scoring systems have not been validated against objective measures of airflow obstruction or disability. Until a method of lung function assessment suitable for home use in this age group is available, overall measurement of symptom severity should include the frequency, duration and magnitude of episodes and interval symptoms.[38] Validation using objective measures is required.

This thesis

More specifically, this thesis aims to clarify a number of the uncertainties described above. These are:

- Is it feasible for young children (and their parents) to inhale a prophylactic drug for several months with a spacer device?
- What are the effects of inhalation therapy of sodium cromoglycate, compared to placebo, on asthma symptoms?
- Is it possible to conduct a clinical trial in general practice in which researchers are responsible for enrolment, inclusion, randomisation and follow-up?
- Is it possible to find determinants of children who still use inhaled prophylactic treatment eight months after finishing the trial?
- What are the reported effects of inhaled sodium cromoglycate in children, in published randomised placebo controlled trials?

The research questions are addressed in the following chapters. Chapter two presents a study investigating whether, and how, children with asthma can be identified in the computerised records of general practitioners in the Netherlands. Subsequently, a randomised placebo-controlled trial of sodium cromoglycate in

218 children with moderate asthma, aged 1-4 years, in the home situation was conducted. Chapter three presents the findings of this trial, and in chapter four the practical aspects involved in patient recruitment, randomisation and follow-up of such a clinical trial in primary care are discussed. The feasibility of inhalation therapy with a spacer device is further investigated in chapter five in which willingness to participate in the trial, loss of participants during the trial and compliance are reported. In chapter six the predictors for use of prophylactic inhalation therapy eight months after finishing the trial in the children that participated are addressed. In chapter seven the findings of all published randomised placebo-controlled trials on prophylactic treatment with sodium cromoglycate in children with asthma are assessed and interpreted in a systematic review. The main conclusions of these studies are discussed in chapter eight in which suggestions for future research are also made. The thesis ends with a summary in both English and Dutch.

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Preschool children with asthma: are they known to their GPs?

Introduction

Since Speight highlighted the underdiagnosis and undertreatment of childhood asthma more than 15 years ago,[1] the subject has been of increasing interest to researchers, clinicians and general practitioners. This is reflected in the publication of various consensus reports during the last few years.[2-5] Consequently, we would expect more children with asthma-like symptoms to be known to their GPs.

The prevalence of asthma in 0-4 year olds is high; rates varies from 5% to 31% according to the definition of asthma and methods of identifying cases used. Several reports have recommended appropriate care[2-5] and some authors have argued that this may improve long-term prognosis.[6-7] In a general practice audit by Levy only one third of asthmatic children had their illness diagnosed before the age of four, despite most having presented respiratory symptoms by this age.[8] By studying GPs' medical records of children, Neville found that 32% were potentially asthmatic.[9] No attempt was made, however, to validate these findings by interviewing parents. Strachan[10] reviewed general practice records of 369 children at seven years of age: 31% had some record of wheeze. After comparing the records with data from parental questionnaires of 174 of these children, the author concluded that parental recall of early episodes is incomplete and biased by the severity and persistence of the symptoms of the child.

In the Netherlands every patient is registered with a general practitioner who acts as gatekeeper to secondary care. This offers a comprehensive sampling base for research into such a prevalent disorder as asthma. We compared GPs medical records of children with parental questionnaires to answer the following question: are preschool children with asthma known to their GP?

Methods

In autumn 1992 parents of all 464 preschool children (1-4 years) of five general practices affiliated with the Department of General Practice of Erasmus University, received a mail questionnaire through their own GP. Two weeks later a reminder was sent to non-responders.
As there is no suitable and well-validated questionnaire for assessing asthma in this age group,[11] we constructed a questionnaire for this objective, adopting validated questions from previously developed questionnaires.[12-14] The questionnaire contained items about asthma symptoms (e.g. wheezing, dyspnoea), past and present asthma medication and morbidity experienced by the child. Based on questionnaire answers, the children were classified as having no, mild, moderate or severe asthma (Table 1). Classification was based on recurrent airway symp-

toms and use of specific asthma medication.[2-5] Peak-flow measurements are not possible in most preschool children. Jones et al. showed that asthma symptoms are closely related to results of lung function tests in children over five years.[12]

We examined general practitioners' records of these children, checking them for asthma symptoms, specific asthma medication, and asthma-related diagnoses (asthma, acute bronchitis, chronic non-specific respiratory disease) since birth. The two people who studied the files were unaware of the answers in the parental questionnaire.
Finally, asthma severity, as based on questionnaire answers, was compared to asthma symptoms, specific asthma medication and asthma-like diagnoses as found in the general practitioners' records. Data were analysed with SPSS-PC. Differences between responders and non-responders were tested by means of a χ^2-test ($p<.05$).

Table 1
Classification of asthma severity according to questionnaire answers

NO ASTHMA
- no respiratory symptoms and no medication

MILD ASTHMA
- dyspnoea at least twice in past 12 months
- wheezing 4 to 12 times in past 12 months
- present weekly use bronchodilators during <6 weeks
- present daily use of deptropine during <6 weeks or deptropine use in past 12 months
- if doctor ever said to parents their child has asthma
- if parents think their child has asthma now

MODERATE ASTHMA
- wheezing >12 times in the past 12 months
- 2 out of 3 of following questions answered 'yes':[8]
  - Wheezy or asthmatic condition ≥1 per week?
  - Hampered in daily activities (feeding, play, going to school or creche)?
  - Wake up from coughing or wheezing during nighttime?
- present use of sodium-cromoglycate or ketotifen
- present use of deptropine during ≥6 weeks
- present daily use of bronchodilators
- present weekly or monthly use of bronchodilators during ≥6 weeks
- use of corticosteroids during <3 weeks in past 12 months

SEVERE ASTHMA
- all 3 following questions answered 'yes':[8]
  - Wheezy or asthmatic condition ≥1 per week?
  - Hampered in daily activities (feeding, play, going to school or creche)?
  - Wake up from coughing or wheezing during nighttime?
- use of corticosteroids during ≥3 weeks in past 12 months
- present use of corticosteroids

Results

The final response to the questionnaire was 87% (404). Analysis of the non-responders showed no differences between responders and non-responders with respect to the GP's recorded information on contact frequency and the presence of asthma-like symptoms, diagnoses and medication. Forty percent of the non-responders were from ethnic minorities (Morocco and Turkey) compared with 14% in the total population ($p<.01$). Presumably these parents had difficulties understanding the questionnaire.

Of the 404 children for whom questionnaires were filled out, 281 (70%) did not suffer from asthma. According to our criteria, 98 (24%) were classified as having mild asthma, 17 (4%) as moderate and 8(2%) as severe asthma.

Asthma symptoms were registered in 35% of the 464 GP files of children 1-4 years of age (table 2). The distribution of these asthma symptoms in the GP files is presented. There is some overlap between different items. Chest congestion with or without sputum production was registered most frequently, followed by wheezing and rhonchi. In nearly 32% of all records the general practitioners prescribed specific asthma medication, including deptropine, an anticholinergic drug which is frequently prescribed in the Netherlands, but uncommon elsewhere.[7] The prescription frequencies of specific asthma drugs are in table 3. For reasons of comparison with other countries, we present figures with and without deptropine. When deptropine prescriptions

Table 2
Number (%) of GPs' files (N=464) containing asthma symptoms

All asthma symptoms	163	(35.1)
· chest congestion/phlegm	74	(15.9)
· wheeze	63	(13.6)
· rhonchi	63	(13.6)
· nocturnal cough	37	(8.0)
· dyspnoea	35	(7.5)

Table 3
Number (%) of GPs' files (N=464) with specific asthma medication

All asthma medication	148	(31.9)
· deptropine	137	(29.5)
All asthma medication (deptropine excluded)	51	(11.0)
· beta-2-sympaticomimetics	34	(7.3)
· ketotifen	30	(6.5)
· ipratropium bromide	7	(1.5)
· corticosteroids	7	(1.5)
· sodium-cromoglycate	5	(1.1)
· xanthines	3	(0.6)

Table 4
Number (%) of GPs' files (N=464) containing asthma related diagnoses

All asthma related diagnoses	93	(20.0)
· acute bronchitis	71	(15.3)
· chronic non-specific respiratory disease	43	(9.3)
· asthma	2	(0.4)

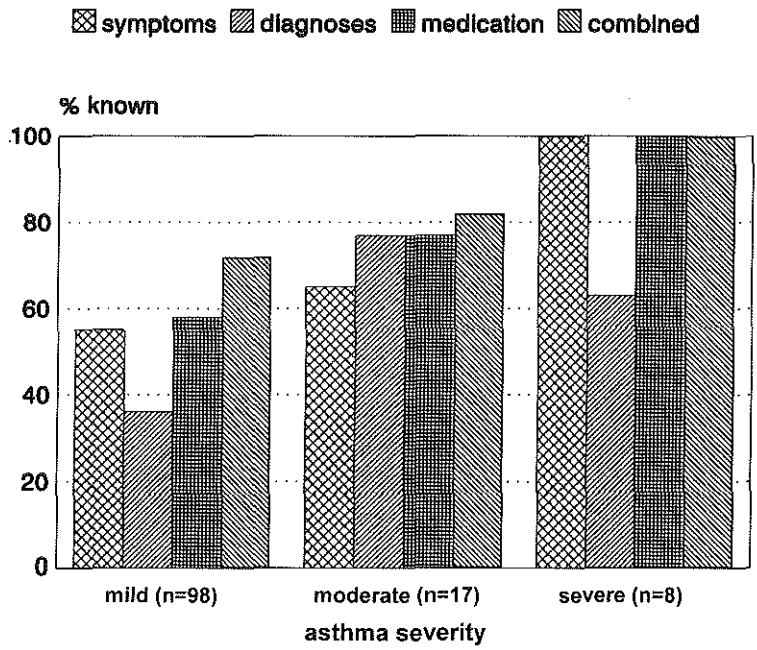

Figure 1
Proportion of asthmatic children known to GP, as indicated by registered symptoms, diagnoses and medication, per degree of asthma severity.

were excluded the prescription of specific asthma medication consequently dropped from 32 to 11%. Asthma related diagnoses were registered by GPs in 20% of the files (table 4). Acute bronchitis was recorded most frequently.

In order to answer the main question we compared questionnaire data with the GPs' records. Figure 1 gives the data from the records for each degree of asthma severity, as found in the parental questionnaire. All children with severe asthma were known to their GP. The proportion drops with falling levels of severity. Asthma-like diagnoses turn out to be registered in fewer children than both asthma symptoms and medication. For all classes of severity combined, 75% of children with asthma are known to their GPs.

Discussion

The return of 87% completed questionnaires was similar to that of other studies on this subject.[10,11]
By focusing on information recorded by GPs, we have restricted ourselves. When asking the GP directly, 'Does this child have asthma?' more cases would probably

have been classified as 'known'. On the other hand, we suspect the latter method of data-collection to be more liable to bias than checking for information that was actually written down during patient care.[15]

In this study, discrepancies between the two sources of information may be explained by the effect of time. As the diagnosis of asthma is seldom made in a single consultation, there may be patients who are still on their way to being diagnosed by their GP among the children we have labelled as asthmatic. Another aspect of time worth mentioning, is reflected in the expectation that many children with airway symptoms will grow out of them, especially in this age group, where viral infections may cause asthma-like symptoms.[16]
Of all items registered by GPs, medication is the best recorded. Recorded asthma medication was mostly deptropine, an oral drug with anticholinergic properties. Use of this drug accords with guidelines for asthma in childhood issued by the Dutch College of General Practitioners.[17] If deptropine had been unavailable (as in other countries), we assume that other drugs would have been prescribed. Antibiotics were excluded from our search, as their prescription for asthma is not advised.

The limited number of practices included in our study means that the conclusions should be generalised with caution. As for the affiliation with the department of General Practice, the chance of selection bias will be small: several hundreds of practices have relations with the department for teaching, vocational training and research activities. None of the practices that participated in this study had been involved in any study in the field of childhood asthma before.

Our results indicate that most children with probable asthma are known to their general practitioners, and that both registered asthma symptoms and specific asthma medication are a more sensitive pointer for detecting children with asthma from GPs' files than specific diagnoses of asthma or asthma-like disorders.

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Randomised placebo-controlled trial of inhaled sodium cromoglycate in 1-4 year old children with moderate asthma

This study was funded by the Netherlands Asthma Foundation (grant no. 93.37). Drugs were provided by Fisons and Boehringer Ingelheim. Spacer devices were provided by Boehringer Ingelheim.

Introduction

Respiratory diseases are an important cause of morbidity in preschool children.[1] The prevalence of asthma and persistent wheeze in children 1-4 years is between 10 % and 20%,[2,3] the variation apparently the result of differing definitions. National and international consensus reports recommend sodium cromoglycate as prophylactic agent of first choice in young children with moderate asthma.[4,5]

Sodium cromoglycate is a safe prophylactic drug that is widely used to treat asthma in children, although its mechanism of action is not fully understood.[6,7] Despite widespread use, the effect of inhaled sodium cromoglycate in very young children with moderate asthma has hardly been studied. Several placebo-controlled trials have been reported but most were hospital-based, studied patients with severe asthma, had follow-up periods shorter than ten weeks, and studied medication inhaled by nebulisation. Six of these studies showed improvement of symptoms in comparison with placebo,[8-13] but in five sodium cromoglycate was no better than placebo.[14-18]

Data on the prescription of anti-asthma drugs in primary and secondary care show a trend of decreasing use of sodium cromoglycate and increasing use of inhaled steroids.[19] Because there is no convincing evidence that inhaled steroids, even in daily doses of less than 400 µg, are without side-effects in the long-term treatment of young children, there is still a potential role for sodium cromoglycate for treating moderate asthma.[20,21] Indeed, König and Schaffer[22] suggested in 1996 (based on a retrospective study) that treatment with sodium cromoglycate improves the long-term prognosis of childhood asthma.

Nebulisation in young children is tedious and time consuming and therefore used mainly in severe asthma. The availability of spacer devices with face masks has extended the use of metered dose inhalers to children of preschool age. In the Netherlands most children with moderate asthma are treated by general practitioners (GPs). Little is known, however, about the feasibility of and compliance with long-term prophylactic therapy when medication is inhaled through a spacer device and facemask at home in young children with moderate asthma.

We undertook a study to investigate these issues in a comparison of inhaled sodium cromoglycate and placebo.

Methods

Children aged 1-4 years who had previously been on medication specifically prescribed for respiratory problems (oral or inhaled bronchodilators, oral or inhaled

steroids, sodium cromoglycate or nedocromil sodium [though the latter is rarely used in young children], ketotifen, deptropine) were selected from the computer files of 151 GPs in the Rotterdam area. On behalf of the GP, we sent a postal questionnaire to each child's parents, enquiring about the child's symptoms and current anti-asthma medication. We defined moderate asthma as one or more of: more than 12 episodes of coughing, wheeze, or dyspnoea during the past year; use of anti-asthma medication; and at least two of the following three during the past month: coughing, wheezing or dyspnoea more than once a week; interference of respiratory symptoms with daily activities; and interference of symptoms with sleep. Children who had been prescribed oral or inhaled steroids or who had been admitted to hospital for acute asthma in the past were classified as having severe asthma. With the GP's approval, the parents of each child classified as having moderate asthma were asked to join the study. Exclusion criteria were congenital disorders and language difficulties (inability to speak Dutch adequately).

Children were enrolled from March 1995, to March 1996, to make sure the trial period included all four seasons. During the first visit, the research physician recorded the child's medical history and condition at that time, examined the respiratory tract, ears, nose and throat, and measured height and weight. The parents gave written informed consent.
Enrolled children entered a baseline period of four weeks, during which only rescue medication (ipratropium plus fenoterol aerosol; Berodual, Boehringer Ingelheim, Germany) was available. If the child was already using prophylactic medication, the baseline period was preceded by a washout period of 3 weeks. At the end of the baseline period the children were randomly assigned inhalation therapy with either sodium cromoglycate or placebo, 10 mg (two puffs) three times daily with a spacer device and facemask (Aerochamber, Boehringer Ingelheim). Study medication (sodium cromoglycate and placebo) was prepared by Fisons plc, Loughborough, UK. We randomised in blocks of six patients and stratified for age, assigning blocks by years of age (1, 2 and 3 years). Parents were provided with rescue medication to be used in case of exacerbation. The study medication was given for five months.

For use of the inhaler, parents were instructed to shake the canister and spray it into the spacer twice, with an interval of 5 s, fitting the facemask tightly around the child's nose and mouth as from the first actuation, and have the child breathe normally for 30 s. We instructed the parents to rinse the spacer device with tap water and allow it to drain, no more than once a week.
During the trial, each child was visited at home once a month by a research nurse. During the visit the nurse checked the inhalation technique with the parents, and asked about respiratory or other symptoms, side effects, difficulties with the spacer device, and visits to the GP or other clinician. Throughout the study,

treatment allocation was concealed from parents, patients, GPs, the research physician, and nurses. Since there is no suitable method of measuring the lung function in this age group at home, symptoms are the most relevant measure of the effect of treatment.[23] We asked parents to fill in a daily symptom-score list (panel) to record their child's asthma symptoms, limitation of activity during the day and at night, and use of trial and rescue medication.
The primary outcome measure was proportion of symptom-free days in month 2 - 5 of the intervention period. Other outcome measures were number of symptoms (possible scores 0-4 per day), use of rescue medication, loss of participants during the trial, need for additional medication, need for GP visits, referrals to secondary care and parent's guess about the type of treatment. We asked parents of children withdrawn during the trial to continue filling in the daily symptom-score list for the remainder of the trial period.

All GPs were advised to prescribe a short course of oral prednisone if asthma symptoms could not be controlled by trial or rescue medication. Reasons for withdrawing from the trial were: more than one exacerbation that had to be treated with oral prednisone; prescription of long-term therapy with inhaled steroids; and hospital admission for exacerbation, adenoidectomy or tonsillectomy.
At the beginning of the trial we weighed a random sample of full canisters of study medication. After the trial all canisters were weighed on the same balance (Mettler AE260 deltarange® Tiel, the Netherlands) to assess compliance.

A pilot study showed that children with moderate asthma had on average 1 symptom-free day in 2, as in a study by Cogswell and colleagues.[9] To detect a difference in proportion of symptom-free days between cromoglycate and placebo of 20% at a significance level of 0.05 and a power of 80%, assuming an SD of 32%, as calculated from baseline symptoms scores, 40 children per group would be needed. We decided to enrol more children to enable the analysis of subgroups.

Questions for daily symptom-score list	
Did you notice your child coughing or wheezing last night?	yes/no
Was your child awake because of coughing or wheezing last night?	yes/no
Did you notice coughing, wheezing or shortness of breath today?	yes/no
Did these airway symptoms interfere with the activities of your child?	yes/no
How often did your child inhale trial medication today?	0/1/2/3 times
How often did your child inhale Berodual today?	0/1/2/3 or more times

The strategy for data analysis was written before the randomisation code was broken. Analysis was done by both intention-to-treat and on treatment. We analysed the main efficacy parameter, i.e. proportion of symptom-free days, by a repeated measures analysis of covariance. This model involved both the mean response over the treatment period (to detect a possible treatment effect) and a linear trend (to detect a possible treatment by time interaction) of dependent variables. Independent variables were test medication (cromoglycate, placebo); gender; seasonal influence (autumn+winter/spring+summer); and smoking by parents; food allergy; eczema; experience with inhalation therapy; and positive family history (all no/yes). Age (months) and baseline value of percentage symptom-free days were used as covariates. Because of a possible violation of the normality assumption, we did the same analysis on arcsinsquare-root-transformed outcome data.[24] Separate analyses of subgroups were done for gender, age, and season. Differences in side effects and secondary effect measures were tested by χ^2 test, *t* tests or Fisher exact tests (two-sided).

The Medical Ethics Committee of Erasmus University Rotterdam/Academic Hospital Rotterdam approved the trial.

Results

2855 children who had previously been on specific respiratory medication were selected from 151 general practices (figure 1). The overall response rate to the questionnaire was 65%. Respondents and non-respondents were similar in terms of age and medication prescribed. 553 children (30% of respondents) met our inclusion criteria for moderate asthma. 104 were not invited to take part, because the GP did not approve the inclusion (mostly because of social circumstances, 20), because we could not contact the parents (43) or because of congenital disorders (three), language difficulties (11), corticosteroid therapy (21), or an adenoidectomy/tonsillectomy planned in the near future (six). 449 children were invited to take part.

Between March 1995, and March 1996, 232 children (42% of those with moderate asthma) entered the baseline period or washout period. 217 children did not start the trial; the parents of 72 children refused to participate because they expected feasibility problems, 109 did not want changes in therapy, 27 did not want any research, and nine refused for unknown reasons. A further 14 children were withdrawn during the washout or baseline period because the inhalation procedure was not feasible (three), the child had an exacerbation of asthma (five), an ear, nose, and throat procedure was planned (two), or other reasons (four). 218 children remained, of whom 109 were assigned sodium cromoglycate and 109 placebo.

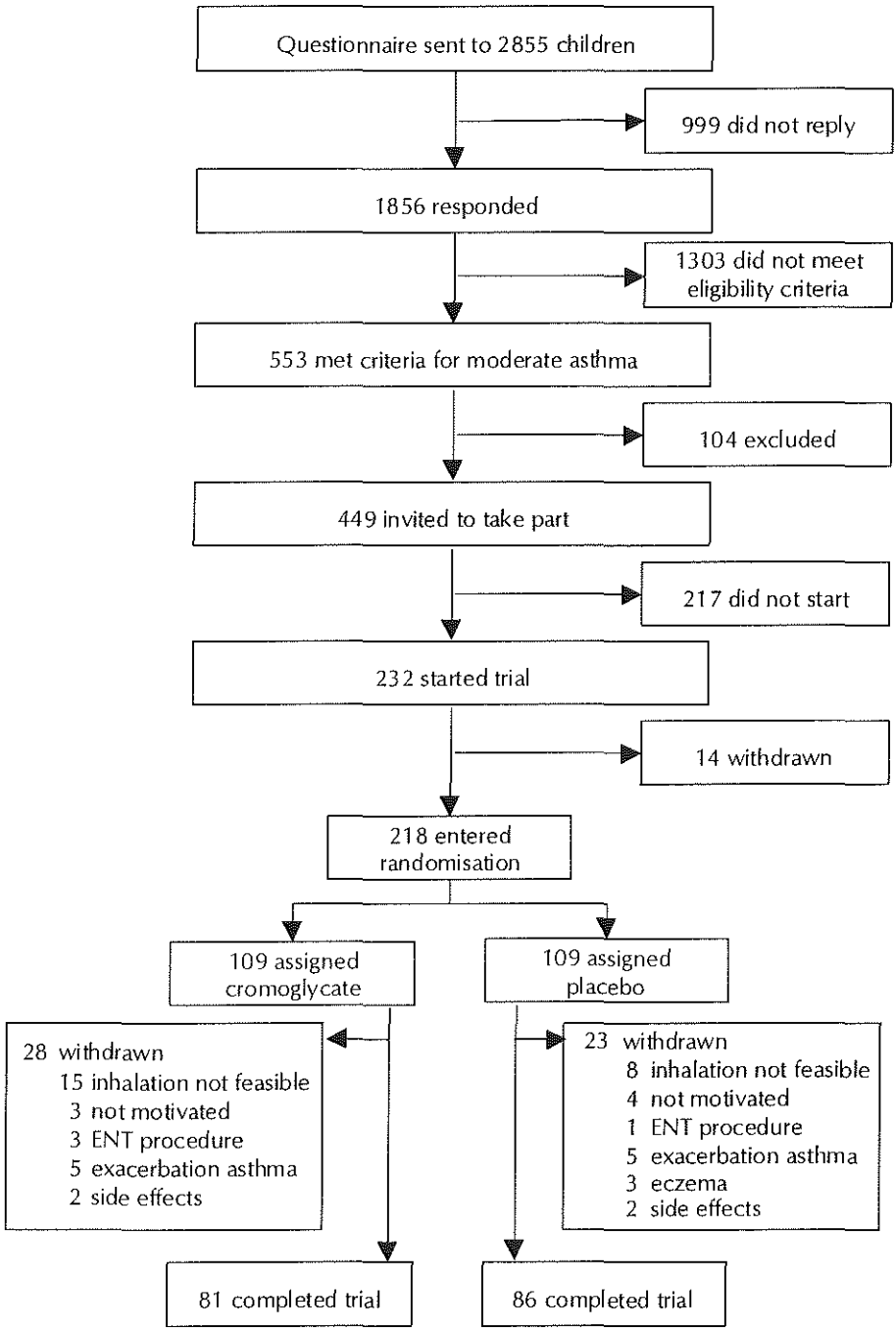

Figure 1
Trial profile

The groups were similar except for baseline symptom score (table 1). During the trial period 51 children (23%; 28 in cromoglycate group, 23 in placebo group) were withdrawn (figure 1). 23 (37%) of the one-year-olds left the trial prematurely, compared with 11 (16%) 2-year-olds, and 17 (19%) 3-year-olds. The main reason for withdrawal of 1-year-olds out was the difficulty parents and children experienced in using the spacer device. Of the children who stopped prematurely, the parents of 38 (23 sodium cromoglycate group, 15 placebo group) kept recording symptoms, although 14 of them registered the daily symptoms for only part of the remainder of the trial period. 13 children (five sodium cromoglycate group, eight placebo group) were lost to follow-up. 167 (77%) children completed the trial.

Table 1
Characteristics of treatment groups at start of trial

	Cromoglycate (n=109)	Placebo (n=109)
Mean (SD) age in years	2.6 (0.9)	2.5 (0.8)
Number aged at entry		
12-23 months	34 (31%)	31 (28%)
24-35 months	32 (29%)	36 (33%)
36-48 months	43 (39%)	42 (39%)
Male/female	58/51	64/45
Medical history		
Mean (SD)% symptom-free days during baseline period	56.5 (31.3)	47.6 (33.2)
Perceived influence of season	50 (55%)	57 (52%)
Eczema	61 (56%)	63 (58%)
Food allergy	48 (44%)	47 (43%)
Asthma also induced by exercise	36 (33%)	36 (33%)
Experience with inhalation therapy	40 (37%)	36 (33%)
Family history of asthma	72 (66%)	58 (53%)
Family characteristics		
Parental smoking	73 (67%)	58 (53%)
Mean (SD) age of mother on day of birth	28.7 (4.5)	28.7 (4.1)
Of non-Dutch origin	5 (5%)	9 (8%)
In day care	43 (39%)	49 (45%)
Mean (SD) position in birth order	1.85 (0.89)	1.94 (0.83)
Education mother low*	66 (61%)	71 (65%)
Education father low*	44 (40%)	41 (38%)
Anthropometry		
Mean (SD) length (cm)	93 (9)	93 (8)
Mean (SD) weight (kg)	15.9 (3.1)	15.5 (2.7)

* ≤ 4 years after primary school

Parents of 40 (37%) children in the cromoglycate group and 33 (30%) children in the placebo group reported side-effects (table 2). No serious side-effects were reported for either group by parents or GPs. Eczema around the place where the mask was applied occurred in five children in the cromoglycate group and none in the placebo group (p=0.052). Nine children in the cromoglycate group and one in the placebo group had coughing after inhalation (p=0.02). The frequencies of other side effects were similar in the two groups.

We estimated compliance from the weights of the returned canisters (mean for cromoglycate group 310 [SE 4] g, placebo group 311 [4] g). Of the children who completed the trial, 66 (81%) in the cromoglycate group and 65 in the placebo group used more than 80% of the recommended dose (p=0.35).

Averaged over month 2 - 5, the proportion of symptom-free days in the cromoglycate group was 65.7% (SD=25.3), compared to 64.3% (SD=24.5) in the placebo group (95% CI for difference, placebo minus cromoglycate, -8.46 to 5.70). In both groups of children, the proportion of symptom-free days improved significantly during treatment (paired t-test, p<0.01; 95% CI, treatment minus baseline, cromoglycate [5.1-17.5], placebo [11.9-23.3]). There was no significant difference in this increase between the groups (figure 2). The 95% CI for the difference between placebo and sodium cromoglycate (percentage symptom free days) adjusted for baseline value was -4.6 to 7.7. Analysis of covariance revealed no significant treatment effect, significant treatment by time interaction, or influence of age, gender, eczema, familiarity with inhalation therapy, seasonal influence or parental smoking on the overall proportion of symptom-free days. Baseline values were predictive of outcome. Analysis of the transformed data gave similar results. On-treatment analysis was done by repeating the tests only

Table 2
Side effects

	Cromoglycate (n=109)	**Placebo (n=109)**
No side effects	69 (63%)	73 (67%)
Behaviour		
More active	6 (6%)	12 (11%)
More sleepy	8 (7%)	5 (5%)
Skin		
Eczema around nose and mouth	5 (5%)	0
Other	7 (6%)	8 (7%)
Cough after inhalation	9 (8%)	1 (1%)
Gastrointestinal	5 (5%)	6 (6%)
Other	5 (5%)	4 (4%)

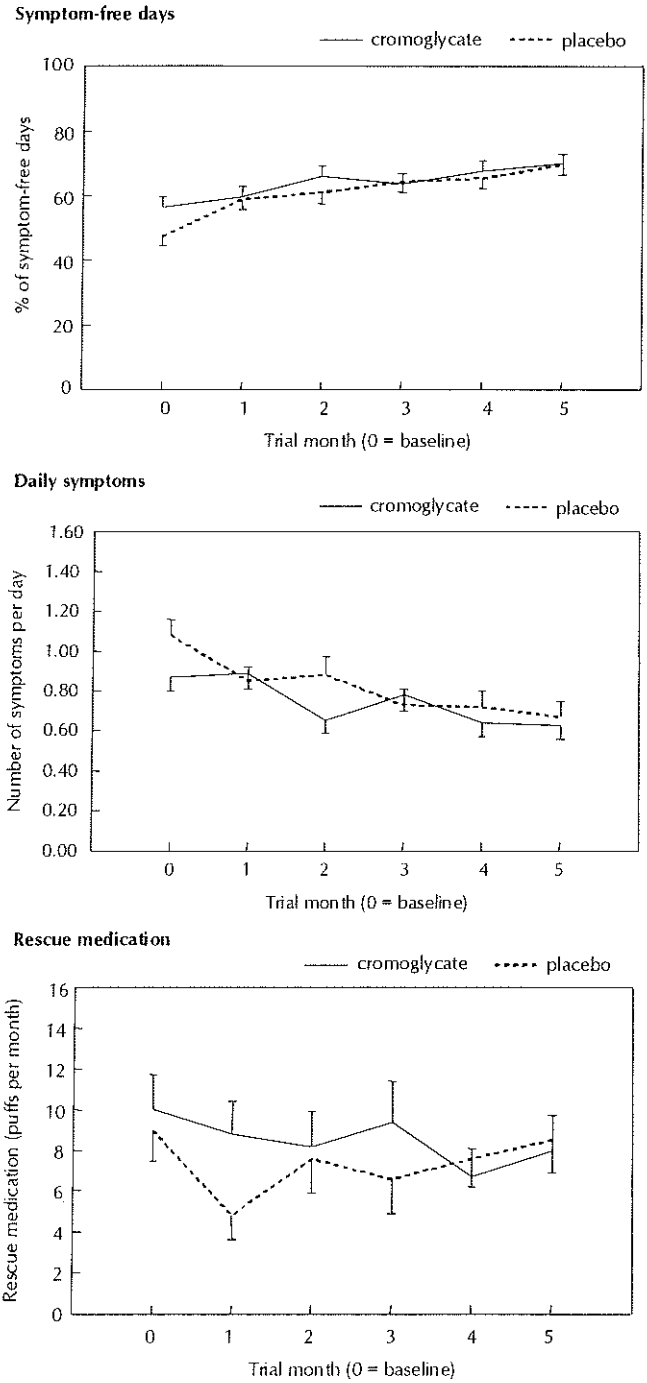

Figure 2
Mean (SE) proportion of symptom-free days, number of symptoms per day, and use of rescue medication

with children who had used more than 80% of the prescribed medication (66 cromoglycate group, 65 placebo group). We could not find any significant differences in outcome (95% CI of difference between placebo and cromoglycate -8.21 to 6.41).

The number of symptoms per day and use of rescue medication per month showed no significant differences between the treatment groups (figure 2). During the trial, parents of children in the cromoglycate group reported 368 episodes of illness, often with respiratory symptoms (164 episodes in 83 children). Parents of children in the placebo group reported 362 episodes of illness, 181 (50%) with respiratory symptoms (88 children). 35 children in the cromoglycate group were taken to their GP about asthma (61 visits), compared with 47 children (85 visits) in the placebo group (p=0.14). Additional medication was used in 29 and 35 children in the cromoglycate and placebo groups, respectively: antibiotics (13 vs. 21), oral steroids (eight in each group), inhaled steroids (three vs. five), deptropine (five vs. six), promethazine (three vs. seven), salbutamol (six vs. one) and ketotifen (three vs. one).

Growth, both linear and in weight, was similar in the two treatment groups during the trial.

29% of the parents of children in the cromoglycate group guessed the treatment correctly, whereas 37% of them thought their child had received placebo. In the placebo group, 30% of the parents guessed the type of treatment correctly, and 33% thought their child had received cromoglycate. The remaining parents did not know.

Discussion

This study of long-term prophylactic inhalation therapy with a spacer device and face mask in 1-4-year-old children with moderate asthma showed that the treatment is feasible at home for such children, 77% of children in our trial used an inhaler for five months, and 78% of users took at least 80% of the recommended dose. Of those who stopped prematurely, 45% had difficulty in using the inhaler, particularly the 1-year-olds. There were no differences in feasibility and compliance between the treatment groups. By contrast, Gibson and colleagues[25] reported poor compliance in a 2-month observational study in young children attending a paediatric respiratory clinic. In a study to assess compliance among adults receiving regular pulmonary medication in a general practice setting, Dekker and colleagues[26] could classify only 30% of the patients as compliant. We think that our better results could be explained by a selection bias of motivated parents and the intensive monitoring by the research nurses.

Both groups improved significantly in the proportion of symptom-free days. This finding can be explained by the placebo effect and the personal supervision associated with a clinical trial, as found previously in many trials in children.
The two groups did not differ in proportion symptom-free days. We could not identify subgroups of children whose response to cromoglycate was influenced by age, gender, positive family history, atopic history, season or smoking habits of the parents. Geller-Bernstein and Levin[11] found an effect of cromoglycate in children aged 12 months and older, whereas no effect was seen in children below this age.

Notable side effects of inhalation of sodium cromoglycate were cough directly after inhalation and eczema around the mouth. The first is well known, the latter was found previously in one of 29 children[15].

The lack of benefit from treatment with sodium cromoglycate in this trial may have resulted from the spacer device we used, which was an Aerochamber. Several studies have shown a higher retainment of medication in this than in other spacer devices,[27-29] so perhaps the dose of sodium cromoglycate reaching the lungs was inadequate in our trial. On the other hand, other studies have shown satisfactory drug delivery by this device in children.[30,31]

There are few published data on assessment and monitoring early childhood asthma, probably because wheezing disorders in young children are ill defined. The limiting factor is our ability to measure the disorder itself. Most clinical measurement schemes are based on symptom assessment, even though symptoms are non-specific and poorly defined and scoring systems have often not been adequately evaluated.[32] However, since symptoms are directly related to the burden of disease, we question whether other, more objective, measures of morbidity would be superior.

We do not think the group size limits our conclusions. We can infer from the 95% confidence interval that the difference between sodium cromoglycate and placebo, if any, is of no clinical importance.
We conclude, therefore, that inhalation therapy three times daily with a spacer device in preschool children with moderate asthma is feasible, and that treatment with sodium cromoglycate via the Aerochamber is no more effective than placebo. We could not show any benefit of sodium cromoglycate treatment that balances the effort and cost of this therapy. Therefore we support the intentions of national and international guidelines committees to withdraw the recommendation of sodium cromoglycate as the first choice in first-line inhaled prophylactic asthma treatment.[33]

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Practical aspects of a randomised controlled trial in general practice; patient recruitment, inclusion and follow-up from an academic centre

Introduction

Randomised controlled trials are increasingly being performed in primary care and contribute to the body of evidence-based medicine.[1,2] Trials in general practice enable collection of data from large populations of patients and, unlike hospital-based studies, provide results that are relevant to clinical practice in a primary care setting.[3] General practice has been promoted as an appropriate setting to evaluate interventions ranging from drug treatment to developments in health care services.[4,5] Morbidity in primary care differs from that in hospital care. Referrals to clinicians are rare for those diseases that occur frequently in general practice.[6] Of all problems presented to the GP, 90% will be treated within the general practice setting.[7] In 1997, 55% of all first prescriptions of drugs for asthma in the Netherlands originated from GPs.[8]

For trials in general practice, two potential roles of the GP are defined: data collector and project leader.[9] When a trial is sponsored by academic units or by industry, as is often the case in multicentre research, the GP generally takes care of recruitment and data collection. This offers the advantage that the logistics and financial planning and conformance with good clinical practice guidelines can be left to others. In Australia, Canada, and the Netherlands, GPs were interviewed about factors affecting their level of interest and activity in primary care research. The results showed that the workload is the most important factor.[10,11] Although, research should involve a minimum of extra work for the GP, the biggest challenge of conducting a randomised controlled trial in general practice is the enrolment of patients.[6,12,13] The GP may be daunted by time-consuming and tedious extra work; instructing the patients, getting informed consent, executing the randomisation, registering baseline and follow-up data, checking compliance, arranging appointments, etc. Actual recruitment usually lags behind the expectations once the trial has started; this phenomenon has been described as Lasagna's law.[14] Trials may be suspended or prematurely ended due to unsuccessful recruitment. An example of a trial that failed because of disappointing recruitment was reported by Tognoni et al.[13] Another study that evaluated 100 (pharmaceutical) multicentre trials in general practice submitted to an ethical committee (1984 - 1989) showed that recruitment of GPs and of patients was 61% and 63%, respectively, of the expected recruitment.[15]

In a primary care setting, we recently conducted a randomised controlled trial of inhaled sodium cromoglycate in 1-4 year old children with moderate asthma. We present the practical aspects involved in patient recruitment and follow-up, and the discrepancies between planning and actuality. By taking over the most time-consuming activities, the workload of the GPs was minimised. We believe that our experiences can contribute to better planning in future research and more successful conduct of trials in general practice.

The study

Brief outline and results

We studied the feasibility and effects of long-term prophylactic inhalation therapy with sodium cromoglycate in preschool children. Children aged 1-4 years with moderate asthma were recruited through GPs in and around the area of Rotterdam between March 1995, and March 1996. After a 4-week baseline period, the children were randomly assigned cromoglycate or placebo, administered by inhaler with spacer device and facemask for 5 months. Parents of the children completed a daily symptom score list. The primary outcome measure, the proportion of symptom-free days for both groups, was greater for the treatment period than for the baseline period. However, there was no difference between the sodium cromoglycate and placebo group, for the proportion of symptom-free days, or for any other outcome measure. A detailed report of this trial has been published elsewhere.[16]

Enrolment, inclusion and sample size

Planned

Children who had previously been on specific respiratory medication were selected from the computerised records of GPs who held these records for at least one year. A pilot study (unpublished data) had shown that children with asthma are best found by conducting a search on specific respiratory medication, rather than a search on asthma diagnosis. On behalf of the GP, we sent a questionnaire to the parents of the selected children, enquiring about the child's symptoms and current medication. With the GPs' approval, the parents of each child classified as having moderate asthma on the basis of the questionnaire, were asked to join the study. In an average practice population of 2350 patients, 75 children aged 1-4 years were expected.[17] The pilot study showed that 5%, i.e. on average 4 children in each practice, would meet the criteria for moderate asthma and two of these would be willing to participate. A study by Cogswell et al.[18] and our pilot study showed that children with moderate asthma have on average 50% symptom-free days. Since the variance of this outcome measure was unknown, we based our calculation of the sample size on the assumption a dichotomous variable, either symptom-free or not on the last trial day. To show an improvement of 20% symptom-free days (i.e. 50 to 70%), with $\alpha = 0.05$ and $\beta = 0.20$, 91 children had to be analysed in each treatment group. We assumed a 40% dropout rate in view of the age of the children, and the intensity and duration of the treatment, and calculated that 150 GPs were needed to include 300 children. During 10 months, 30 children had to enter the trial each month.

Actual

Enrolment of GPs preceded the enrolment of children by 3 months. A total of 160 GPs were asked to participate. They received an explanatory letter before being telephoned by the research physician (also a GP). Seven GPs were excluded because they were not computerised at that time. Only two GPs refused to participate, stating that they were not interested in asthma. Thus, 151 GPs, located in 109 practices, agreed to participate. Of these, 81 had a solo practice, 36 worked together with one colleague and 34 GPs worked in 10 group practices. An average of 4 (range 1-10) telephone calls was needed to make the first appointment with a GP, in which mostly the computerised patient files were searched immediately. The mean number of children below four years of age was 160 (sd=100), i.e. 4.9% (range 2.0-9.0, sd=1.6) of the practice populations (data from 61 practices). The mean number of children with a prescription for anti-asthma medication selected in each of 109 practices was 26 (sd 20), i.e. 20% (range 3.0-50.0, sd=11) of all children under the age of four (known for 61 practices). Questionnaires were sent to the parents of 2855 children asking about the child's symptoms and current medication. The percentage responders of the questionnaires sent to parents of the selected children was analysed by type of general practice (i.e. solo practice, duo, group) and urbanisation (city, town, village) in a linear regression model, both univariate and multivariate. Because of a possible violation of the normal assumption, the percentage responders was transformed (arc-sin-square-root-transformation).[19] The overall percentage respondents was 65.3% (range 12.9-100, sd=13.8). The response rate among patients of solo practices was 66.9% and of duo- and group practices 62.7% and 56.5%, respectively. The difference was significant ($p<0.05$). Urbanisation was not a predictor of percentage responders.

The mean number of children in each practice who met the criteria of moderate asthma was 5.1, (range 0-22, sd 4.2). Six GPs vetoed the participation of 20 children, mainly due to adverse social circumstances; we were unable to contact the parents of 43 children, and 41 children met an exclusion criterion. A total of 449 children were then invited to participate; a letter was sent to the home before being telephoned by the research physician. Finally, 232 children (52%) started the baseline period and 218 (49%) were randomised; of these, 51 children (28%) stopped prematurely. On average 2 children from each practice were randomised (range 0-10, sd=2), 1.4 child per GP. Figure 1 shows the expected and actual patient inclusion and withdrawal. Because inclusion was slower than expected we extended the enrolment period from 9 to 12 months. We also recalculated the sample size because the premature dropout rate was lower than expected. The variance of the proportion of symptom-free days in the baseline period of the first 90 children, enabled us to recalculate the sample size with a more appropriate formula.[20] Assumptions for improvement, α, and β remained the same. The recalculation revealed that only 40 children would be needed in

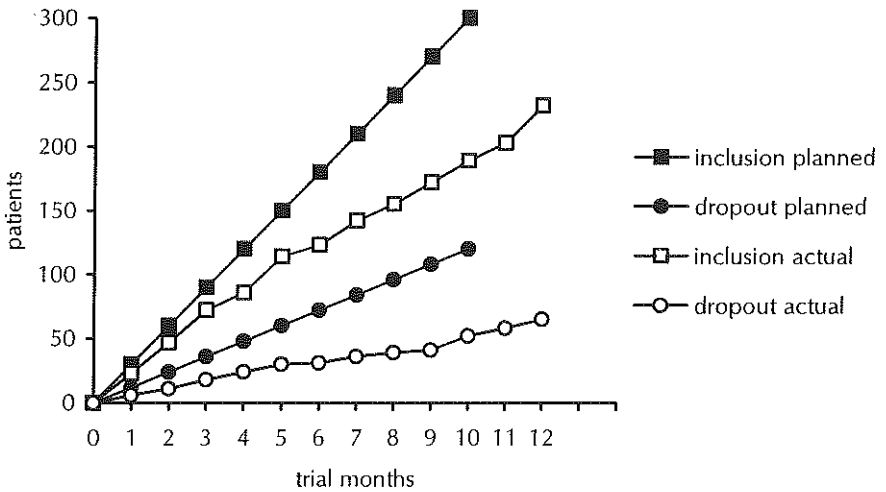

Figure 1
Patient inclusion, planned and actual

each group; we decided to continue recruitment to increase the power of subgroup analyses.

Randomisation

Planned

After the baseline period the children were randomised (based on order of entry) to either sodium cromoglycate or placebo, stratified for year of age. Medication was prepared by the pharmaceutical industry (in blocks of six) and blocks were assigned by year of age. Two copies of the full randomisation list were obtained, both in sealed envelopes; one was stored at the trial centre, the other was kept at the practice of one of the GPs. Furthermore, separate sealed envelopes for each randomisation number were stored in a similar way.

Actual

A total of 218 children were randomised. During the trial the code was broken twice, because hospital consultants considered it necessary to know the child's treatment in order to decide follow-up treatment after termination of the trial. The randomisation presented no other problems.

Follow-up

Planned

During the first home visit, the research physician explained the trial to the parents, asked informed consent, and recorded the child's history and condition. If

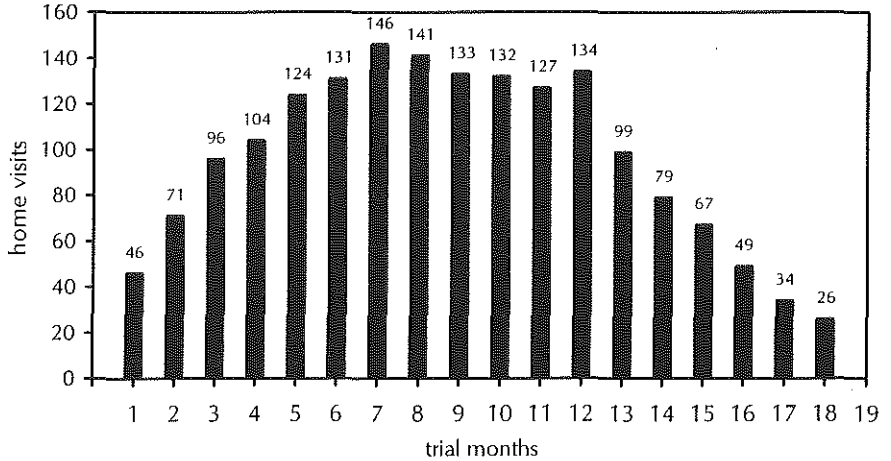

Figure 2
Home visits during the trial

the child was already using prophylactic medication, the baseline period was preceded by a washout period of 3 weeks. During the trial period each child was visited at home once a month by a research nurse who checked inhalation technique, symptom score lists, asked about condition and side effects and provided the medication for the next month. The GP stayed in charge of primary care; he was advised by the research physician to prescribe a short course of oral prednisone if asthma symptoms could not be controlled by trial or rescue medication. Throughout the study, treatment allocation was concealed and GPs were informed several times about their patient and the trial.

Actual

During the baseline period 14 children dropped out, they were visited only twice. The 218 randomised children were visited 8 times at home, first by the research physician and subsequently by the research nurse: once prior to the baseline period, once at the start of month 1 (randomisation) and subsequently at the end of each trial month until the end of the fifth month. During the trial, 51 children dropped out prematurely. Of these, 38 parents continued to record symptoms and 13 parents did not. The research nurses made 14 additional visits because spacer devices were lost or defect, or side effects were reported that needed an immediate check. A total of 1737 home visits were made (figure 2). A home visit generally took 30 to 60 minutes. The mean distance for a home visit was 18 km, amounting to 68000 km during the trial. One research nurse was occupied for 20 months, a second nurse for 8 months. They both worked 80% and on average made four home visits per day, conducted appointments, mailings, data entry, etc.

The GPs were updated at least four times about their patients; at inclusion, after randomisation, during the trial, and at the end of the trial period. In addition, three newsletters were sent to all GPs reporting of trial progress and preliminary results. Finally, all GPs received a reprint of the published results.

Comment

Although adjustments were made in the recruitment phase, we conclude that this randomised controlled trial in general practice worked out well. Our planning underestimated the logistics of recruitment of GPs and subsequent patient recruitment, and we did not allow for a moderate response rate to the questionnaires. It was necessary to extend the recruitment period by three months; instead of 2 eligible children per participating GP, we actually recruited 1.4 child per GP. On the other hand, the sample size and the dropout rate were lower than expected. Currently, in the Netherlands 80% of GPs employ electronic medical records.[21] Most of the invited GPs agreed to participate (99%), probably because of our assurance that their extra workload would be minimal. The percentage responders was lower for patients of GPs working with colleagues than for solo practice GPs. This finding could not be confirmed by other reports, but an explanation could be that patients feel more obliged towards a solo practice GP.

We conclude that this trial was successful mainly because of a relatively passive role for the GP. This was reached in three ways. Firstly, we were almost independent of the GP in recruiting children; the research physician searched the GPs electronic medical records for data on prevalent illness. From then on all activities necessary for recruitment were steered by the researchers. An example of another trial with cases selected from data on prevalent illness is that reported by Walma and colleagues;[22] they included 202 patients receiving long-term diuretic therapy, identified by scanning the pharmacy registers of general practices. Especially in general practice, trials with patients that can be selected by diagnosis or medication already prescribed may be more successful in recruiting patients than trials that evaluate interventions of incident diseases. Peto and colleagues[23] asked GPs to recruit patients requiring treatment for menorrhagia and a review of six general practices revealed that only 20% of the 196 eligible patients had been recruited. Secondly, we were independent of the GP in collecting data from the participants during the follow-up period. All contacts were arranged directly between the research physician or nurse and the parents. Although we conducted instructions, medication distribution and randomisation, the GPs stayed in charge of primary care and were well informed about their patients throughout the trial. Thirdly, all patients were visited at home. In a trial investigating otitis media, young children had to report to a clinic for a diagnostic proce-

dure; problems with transportation, lack of time and lack of care for other children were reasons for parents not to participate.[24] Volmer and colleagues[25] recruited families of children with asthma; only 55% of the children scheduled for randomisation visits in the clinic attended the initial appointment. There are other advantages in being independent of the GP at an early stage of the trial. For external validity of the study results it is important to record the selection of eligible patients in the phase prior to inclusion.[6,26] We were able to give a uniform report on the difference between eligible and enrolled patients because we had contacted all respondents. The degree of willingness of GPs to participate does not guarantee enrolment of eligible patients; Kuyvenhoven et al.[26] reported that 24% of the GPs who participated in their study on sore throat enrolled no patients at all. In the clinical trial prepared by Tognoni and colleagues[13], on the treatment of isolated systolic hypertension in the elderly, 806 GPs agreed to participate but only 63 started recruitment activities; the authors suggest that the change in attitude of GPs from the role of reassuring prescriber to one of uncertainty led to withdrawal of GPs. This factor may also be reduced when the researchers take over all pragmatic aspects of the trial. Randomisation must be centralised; in most multicentre trials this is best done by telephone or by a computer link.[27] In our case, the researchers were directly responsible for the randomisation without interposition of the GP.

We conclude, therefore, that our approach of conducting a randomised controlled trial in general practice was successful because we recruited from computerised data on prevalent illness, and undertook the tasks of recruitment, inclusion and follow-up without bothering the GP.

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Feasibility of long-term inhalation therapy in preschool children with moderate asthma

Introduction

Current guidelines recommend inhalation therapy as the preferable way to administer medication to children with asthma.[1] The availability of spacer devices with face masks has extended the use of metered-dose inhalers (MDIs) to children of preschool age. The preference for an MDI with spacer and face mask above a nebuliser is reflected in guideline recommendations for preschool children.[1] Studies have shown that spacer devices are as effective as nebulizers.[2,3] Various spacer devices with face masks are available and the delivered dose varies considerably between devices and intended age groups. The choice of spacer depends mainly on convenience, compliance and parental preference.[1] Especially in young children adherence to therapy largely depends on parental commitment.

Achieving control in children with asthma is difficult, as reflected in increasing morbidity and hospitalisation rates, and the increasing use of effective anti-inflammatory therapies.[4-7] There are many reasons for a poor response to treatment, but one increasingly recognised problem is failure to adhere to the prescribed treatment. Compliance and patient/parent-adherence have been underexposed, partly because methods of measuring compliance are often inadequate.[8,9] Data on the feasibility of inhalation therapy in young children are even scarcer; in this case the selection of children and their tolerance of the spacer device are important issues. Nonadherence has considerable consequences for morbidity, clinical trial outcomes and costs of treatment.

Compliance with inhaled asthma treatment is generally poor. The extent to which asthma patients follow prescribed treatment plans is reported to range from 30 to 70%.[8] After reviewing the prescriptions of nearly 18,000 children (aged 4-17 years) with asthma, Warner showed that 52% had been prescribed preventive treatment but only 15% received sufficient repeat prescriptions to suggest that they regularly adhered to the treatment.[5] Another study reported a compliance rate of almost 60% in children receiving prophylactic medication during 13 weeks.[10] Gibson et al. hypothesised that parental involvement in drug administration to preschool children would result in better compliance, but reported poor results with inhaled prophylactic therapy during two months in 26 children attending a hospital; they suggested that their results might even have overestimated true compliance.[11]

Little is known about the feasibility of and compliance with long-term prophylactic inhalation therapy through a spacer device and facemask in young children. Therefore, we investigated the feasibility of and compliance with 5 months of inhalation therapy, 3 times daily, in 1-4 year old children with moderate asthma.

Methods

The study question was addressed within the context of a randomised trial of sodium cromoglycate that has been reported elsewhere.[12] The Medical Ethics Committee of Erasmus University/University Hospital Rotterdam approved the trial. Children with moderate asthma were selected from computerised medical files of general practitioners (GPs) in the Rotterdam area, containing data on prescribed asthma medication and recorded asthma symptoms. Children who had been prescribed oral or inhaled steroids were classified as having severe asthma and were not approached. The parents of children classified as having moderate asthma were asked to participate in the study; they received a letter before they were telephoned and visited by the research physician. The participating parents gave written informed consent. Children who were enrolled entered a baseline period of four weeks after which they were randomly assigned to inhalation therapy with either sodium cromoglycate or placebo, three times daily 10 mg (two puffs), using a spacer device and face mask (Aerochamber®). Parents were provided with rescue medication (ipratropium+fenoterol aerosol (Berodual®)) to be used in case of exacerbation. The trial was designed to cover a 5-month period. To use the inhaler, parents were instructed to shake the canister and spray it into the spacer twice, with an interval of five seconds, fitting the face mask tightly around the child's nose and mouth from the first actuation, and have them breathe normally for 30 seconds. Parents had to fill out a daily symptom score list recording the child's asthma symptoms and limitation of activity during the day and night, and use of trial and rescue medication. During the trial the children were visited once every month at home, the first time by the research physician and subsequent visits by a research nurse. During each visit the nurse checked the inhalation technique with the parent(s), asked about respiratory or other symptoms, side effects, concurrent medication, problems with the spacer device, and visits to the GP or clinician. The child's medication for the subsequent month was delivered at each visit. Eight months after the trial period, parents of all children were interviewed by telephone about symptoms and medication. During the trial, GPs were advised to prescribe a short course of oral prednisone if asthma symptoms could not be controlled by trial or rescue medication. Reasons for withdrawing from the trial were: more than one exacerbation treated with oral prednisone; prescription of inhaled steroids; hospital admission due to exacerbation, adenoidectomy or tonsillectomy. Parents of children who dropped out or were withdrawn during the trial were asked to complete the daily symptom score list for the remainder of the trial period.

Fifty full canisters, a random sample of the study medication, were weighed; variation in weight was negligible (sodium cromoglycate: mean= 25.86 g sd= 0.070 g, placebo: mean= 25.73 g sd= 0.097 g). After the trial all canisters were

weighed using the same balance (Mettler AE260, Deltarange®, Tiel, the Netherlands).

Outcome measures used to assess feasibility were willingness to participate in the trial, loss of participants during the trial, and percentage of medication taken (both reported by the parents and calculated for weighing canisters).

Compliance was calculated for all children who completed the trial. We defined *weight compliers* as subjects who used at least 80% of the prescribed dose based on the weight loss of the canisters, and *note compliers* as children who used at least 80% of the prescribed number of puffs as reported by the parents on the daily score lists. To compare our results with other studies we calculated day compliance (the proportion of days of strict adherence to the prescribed regimen) and dose compliance (administered doses as a proportion of total prescribed doses over the entire study period).

The influence of patient characteristics on premature withdrawal and on compliance, according to the definitions above, was evaluated by means of a logistic regression analysis with age, gender, medication (placebo/cromoglycate), side-effects, eczema, food allergy, birth order, age and education level of mother, age and education level of father, smoking habits of the parents, day care, family history and baseline severity as explanatory variables. To evaluate how much variation in the number of puffs reported by the parents could be explained by weight loss of the canisters, a Poisson regression analysis was carried out.[13] For each patient, we computed the mean number of reported doses per day and the mean number of doses per day estimated from the weight loss of the canisters; the relationship was tested with a Wilcoxon signed rank test. Mann-Whitney tests were used to analyze the relation between compliance and the experienced episodes of respiratory illness, as reported during the home visits. We evaluated whether the number of symptoms on the same and the previous day predicted the compliance, by a logistic regression for repeated measurements (SAS Proc Genmod).

Results

The effectiveness of sodium cromoglycate in this trial has been reported in detail elsewhere; no differences were found between sodium cromoglycate and placebo treatment.[12]

From medical records of 151 general practitioners, 553 children met our criteria for moderate asthma. Of these, we invited 449 to participate in the trial and finally 232 children entered the baseline period. Reasons for not being invited and not participating are listed in Table 1. Participants and non-participants were

comparable with regard to age, gender and medication prescribed. Fourteen children dropped out during the baseline period; of the remaining 218 children, 109 were randomised to receive sodium cromoglycate and 109 to receive placebo.

Table 2 lists the patient characteristics. During the trial period, 51 children (28 in the cromoglycate group and 23 in the placebo group), dropped out or were withdrawn for similar reasons in both groups. In total 37% of the one-year-olds dropped out prematurely, compared with16% and 19% of the two- and three-year-olds, respectively. The main reason for withdrawal of the one-year-olds was difficulty in using the spacer device (Table 3).

Characteristics of withdrawals due to feasibility problems were younger age (year) of the child (odds ratio= 2.6, p=0.003), and lower education level (low versus high) of the mother (odds ratio= 5.0, p=0.013). Gender, eczema, food allergy,

Table 1
Reasons for non-participation and non-completion of the trial (Values are numbers of children)

Returned questionnaire and classified as moderate asthma		**553**
Not invited	**104**	
No contact parents	43	
Disapproval GP	20	
Exclusion criteria:		
· congenital disorders	3	
· language problems	11	
· on steroid therapy	21	
· planned ENT procedure	6	
Invited to participate in the trial		**449**
Parents not willing to participate	**217**	
Expected feasibility problems	72	
Wanted no changes in current treatment policy	99	
Recent ENT procedure	10	
Wanted no research, feared side effects	27	
Unknown	9	
Started baseline period		**232**
Dropped out	**14**	
Feasibility problems	3	
Medical reasons	7	
Other	4	
Randomised		**218**
Dropped out	**51**	
Feasibility problems	30	
Medical reasons	21	
Completed the trial		**167**

birth order, age of mother, age or education level of father, smoking habits of the parents, family history, day care, baseline severity, side-effects or medication (cromoglycate or placebo) were not related to withdrawal. Finally, 167 children completed the study.

Weight compliance

Of the 167 children, 131 (78%) used over 80% of the recommended dose. Presence of eczema (odds ratio = 2.6, p= 0.019) was a significant predictor of better compliance. No other patient characteristics had any influence on compliance.

Note compliance

Parents of 119 (71%) children registered that 80% of the total prescribed dose had been taken. None of the patient characteristics showed a significant odds ratio, although eczema yielded a borderline significant result (odds ratio = 2.1, p=0.055). The proportion of days of full adherence to the prescribed dose (day compliance) was 62%, and the proportion of the total dose actually administered over the entire study period (dose compliance) was 81%. Table 4 shows a cross-tabulation of note compliance and weight compliance; agreement in classification was found in 84% (Kappa = 0.59, SE=0.071, p<0.001).

Table 2
Patients' characteristics

	Cromoglycate	Placebo	Total
Age in years; mean [sd]	2.6 [0.9]	2.5 [0.8]	2.6 [0.8]
Male (%)	53	59	56
Eczema (%)	56	58	57
Experience with inhalation therapy (%)	37	33	35
Education mother low (%)	61	65	63
Education father low (%)	40	38	39

Table 3
Reasons for withdrawal according to age of the children

	Age		
	1 year	2 years	3 years
Number of children in trial	**63**	**69**	**86**
Number of children withdrawn	**23 (37%)**	**11 (16%)**	**17 (19%)**
Feasibility problems	17 (27%)	7 (10%)	6 (7%)
Medical problems	6 (10%)	4 (6%)	11 (12%)

Table 4
Comparison of 80% compliance based on canister weight loss versus parent reports.
(Values are numbers of children.)

		Weight complier		
		no	yes	
Note complier	no	29	19	48
	yes	7	112	119
		36	131	167

Relation between note compliance and weight compliance

The Poisson regression yielded an R^2 of 0.64, indicating that 64% of the total variation in the registered number of puffs could be explained by the estimated relation with final weight loss of the canisters. Figure 1 shows individual mean reported daily dose versus the daily dose calculated from weight loss. The mean daily dose of trial medication was 2.5 times 2 puffs per day (sd=0.5) as registered by the parents. Again, there were no significant differences between the two treatments. The mean daily dose based on weight was 2.7 times two puffs per day (sd=0.9) (Wilcoxon rank test $p<0.0005$). The number of symptoms predicted compliance with preventive medication on the same day (odds ratio: 1.1 per symptom, $p=0.015$), which means an every symptom increased the odds on compliance by 10%. A similar relation was shown when the number of symptoms on the previous day was taken as a predictor (odds ratio: 1.1, $p=0.011$).

In 29% of the (5x167=835) home visits during the treatment period parents reported respiratory episodes in the previous month. Parents of weight compliers reported more respiratory episodes (mean 1.6) than non-weight compliers (mean 1.1) (Mann-Whitney test $p=0.03$).

Eight months after the end of the trial we interviewed the parents of 208 children by telephone. Of them, 90 judged the asthma status of their child to be the same as or worse than in the previous year; 104 children still used inhaler medication administered with a spacer device (mostly an Aerochamber®); 44 children used inhaled preventive medication and 84 children used inhaled bronchodilators.

Discussion

This study on long-term prophylactic inhalation therapy with a spacer device and facemask in a large group of children (aged 1-4 years) with moderate asthma showed that such treatment is feasible in selected children. Nearly 80% of the

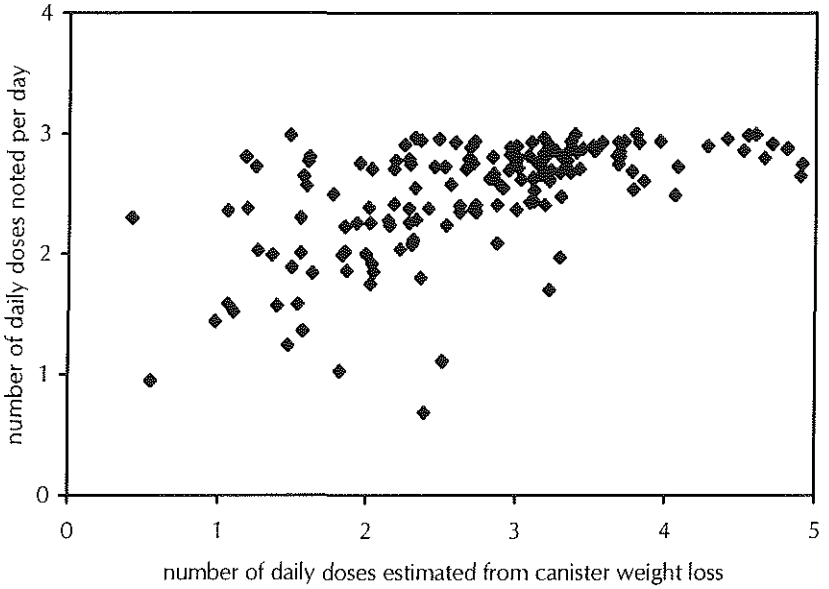

Figure 1
Plot of individual mean reported daily dose versus the daily dose as calculated from weight loss

children used more than 80% of the medication prescribed. Compared with similar data on this age group, this compliance rate is rather high. Gibson et al. found a variable and often poor compliance with inhaled prophylactic therapy in their hospital-based study in preschool children.[11] They observed 26 children during 2 months and used diaries and electronic timers to assess compliance; they reported a day compliance of 50% and a dose compliance of 77%. In our study, day compliance and dose compliance were 62% and 81%, respectively, during 5 months. Coutts et al. measured compliance in 14 asthmatic children, (aged 9-16 years), during 1 to 3 months by means of diary cards and electronic devices; they found under-use of inhaled prophylactic medication in 55% of the study days.[14] Milgrom et al. found the median actual use of inhaled steroids to be 58% in 24 children aged 8-12 years.[10]

The good compliance in our study may be attributed to three factors. Firstly, in the recruitment phase prior to randomisation, selection based on parental motivation was made. Of all eligible children whose parents did not participate, 32% refused because they expected feasibility problems. Secondly, during the trial, 59% of the children who prematurely ended the intervention period, withdrew because of feasibility problems. Thirdly, participation in the trial probably improved compliance with treatment[15] due to regular home visits, and detailed information about the therapy.

On the other hand, sodium cromoglycate treatment showed no beneficial effect compared to placebo and the prescribed regimen of trial medication was demanding: 3 times daily 2 puffs. It has been reported that regimens involving dosing once or twice daily result in better compliance.[14,16,17] Gibson et al.[11] did not find this relationship, but in case of 3 prescriptions daily the middle dose was often omitted; the same result was shown by Milgrom et al.[10] for inhaled steroids in children.

Measuring compliance is difficult; the most common measures used to assess patient adherence with asthma therapy are self-report by diaries, electronic measurement and medication measurement. An electronic timer device counts and times each actuation of an MDI and can be used with all types of aerosol canisters allowing direct monitoring of inhaler use. Both weighing and electronic measuring can be confounded by actuations into the air, e.g. test firing before actual inhalation of drug or canister dumping by successive firing.[8,9] Braustein et al. used all three measurements and found that both canister weight and patient reports overestimated compliance compared with the electronic device. Apart from physician assessments, patient diaries may be less reliable than other measurements because over-reporting by the patients and by parents is common.[10,11,14,19-20] Strikingly, in our study the parents under-reported the use of medication compared with canister weights. This under-reporting was expressed by the difference between note and weight compliance (Table 4), by mean daily dosages based on parents' reports and weights (2.5 versus 2.7), and by the scatter diagram of individual points (Figure 1). The points on the right side of Fig.1 probably represent test firing or canister dumping, rather than overdosing. None of the parents reported more than three daily doses, because the score list did not provide for this option.

Our study shows a weak, but significant relation between compliance of inhaled prophylactic medication and number of symptoms on the same day and the previous day: every symptom increased the odds on compliance with 10%. We realise that due to the large study population and the large number of trial days our test was powerful. It is likely that symptoms alert the parents to give medication. Also, the reported respiratory episodes were a predictor of better compliance. Apparently, parents of young children with moderate asthma who are reminded by their child's symptoms will become more compliant in administering prophylactic medication to their child. Other studies show no relation with symptoms.[11,21] In the study by Milgrom et al.[10] compliance with inhaled steroids showed that low compliance was associated with exacerbation of asthma.

The unpopularity of preventive medication, rather than unpopularity of method of administration, was demonstrated by our follow-up data. Although 43% of the parents indicated that their child had the same or worse symptoms during the

eight months after the trial period, nearly all used a spacer device with facemask for their bronchodilators, but only 21% still used preventive inhaler medication. Moreover, 76% of the parents indicated they preferred to use bronchodilators more often rather than use preventive medication for their child every day.

To our knowledge, this study is the first to establish the presence of eczema as a predictor of better compliance; parents may be extra motivated by seeing the child with symptoms of a related disease. No other patient characteristics, or baseline severity and medication (placebo or cromoglycate) were predictive of note compliance or weight compliance. In the study by Gibson et al.[11] day care had a significant adverse effect on dose compliance but not on day compliance, indicating a poorer overall parental compliance in children who attend day care. In our study, whether children were cared for at home or nursery had no significant effect on drug administration.

We conclude that long-term inhalation therapy with spacer device and facemask is feasible in selected 1-4 year olds and that compliance can be relatively high in a selected and well-supported group. Lower age of the child and lower education level of the mother are risk factors for treatment failure. Children who experience more respiratory symptoms or have eczema show better adherence to the prescribed regimen.

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Adhesion to long-term asthma prophylaxis in preschool children

Introduction

Many young children have one or more episodes of wheezy breathing before the age of four, often associated with viral respiratory illnesses.[1] Two thirds of these children, especially those with milder symptoms, will not have asthma after the age of six.[2] Apart from symptoms, there are no suitable tests that can routinely be applied at preschool age. Therefore, it is important to assess the relationship between the pattern of morbidity and disease evolution, including compliance with treatments. The aim of our study was to investigate whether predictors of long-term adherence to inhaled asthma prophylaxis can be found in young children with moderate asthma in general practice.

Patients and methods

Children aged 1-4 years, recruited through 151 general practitioners (GPs) between March 1995 and March 1996, participated in a randomised placebo controlled clinical trial that evaluated the effects of sodium cromoglycate inhalation therapy by means of a spacer device and face mask, during 5 months.[3] The diagnosis moderate asthma was based on prescriptions of anti-asthma medication in the past, and on symptoms and medication at entry. At the beginning of the trial, the child's medical history was recorded and during the trial parents daily recorded their child's respiratory symptoms and use of rescue medication (bronchodilator). During monthly home visits by a research nurse, the parents were asked about visits to the GP. The detailed methodology and results of this trial have been reported elsewhere.[3] After the trial, continuing prophylactic treatment was decided by the patient's own GP and not influenced by the research team. Fourteen months after the baseline assessment (8 months after the trial) the parents were contacted by telephone and follow-up data were obtained about asthma medication during the previous six months. We compared children who still used inhaled prophylaxis (cromoglycate or steroids) 14 months after start of the trial with those who had been without prophylaxis with respect to patient characteristics (age, gender), data recorded at the start of the trial (height and weight, provocation of symptoms by exercise, siblings with asthma, history of parents for asthma and atopy, reported eczema and food allergy, attendance at day-care, parental cigarette smoking) and morbidity characteristics during the trial (sum of symptoms per day, percentage of symptom-free days, use of inhaled bronchodilator per day, number of episodes, duration of episodes, number of GP consultations for respiratory and non-respiratory reasons). An asthmatic episode was defined as a period of at least 4 consecutive days with at least 3 out of 4 symptoms each day. Finally, the number of children receiving cromoglycate during the trial was compared for both groups. The differences were tested by

means of logistic regression analysis. We calculated odds ratios with 95% confidence intervals (CIs).

Results

Of the 218 children who had participated in the clinical trial 208 were reached by telephone eight months after the trial had finished. We were unable to trace 10 children whose age, gender and other outcome measures for asthma symptoms during the trial were similar to the children contacted. Of these 208, 44 children were still using prophylactic inhalation therapy. Data of this latter group were compared with those of 164 children who were without prophylaxis. Figure 1 shows the differences between the groups with odds ratios and 95% CIs. Characteristics not mentioned in Figure 1 were similar for both groups.

Discussion

In this study, 21% of the children had continued prophylactic inhalation treatment 14 months after the start of the trial. To our knowledge this study is the first to investigate to what extent morbidity characteristics of preschool children with moderate asthma predict long-term adherence to inhaled prophylactic treatment. The differences found in morbidity characteristics suggest that these children initially had more troublesome symptoms: longer and more frequent respiratory episodes, more frequent use of bronchodilators and more frequent consultations for respiratory complaints, whereas the overall main outcome measures of the trial (proportion symptom-free days and sum of daily symptoms) were similar in both groups. A surprising finding was that children on inhaled prophylaxis at follow-up were less likely to have attended day-care. We speculate that the more troublesome the disease is, the less likely that the parents will arrange day-care for their child. Another explanation might be that children who attended day-care had more infections and therefore less asthma at follow-up.[4]

Several large cohort studies have shown that the more severe the asthma, the less likely it will be outgrown.[2,5-7] Exercise as a provoking factor for asthma symptoms[5] and asthmatic parent(s) have been recognised as risk factors for persisting asthma.[2,6]

We conclude that several characteristics from history and morbidity in preschool children with moderate asthma in a general practice setting predict adherence to prophylactic inhalation therapy after 14 months, and that these correspond with known risk factors for persisting asthma symptoms.

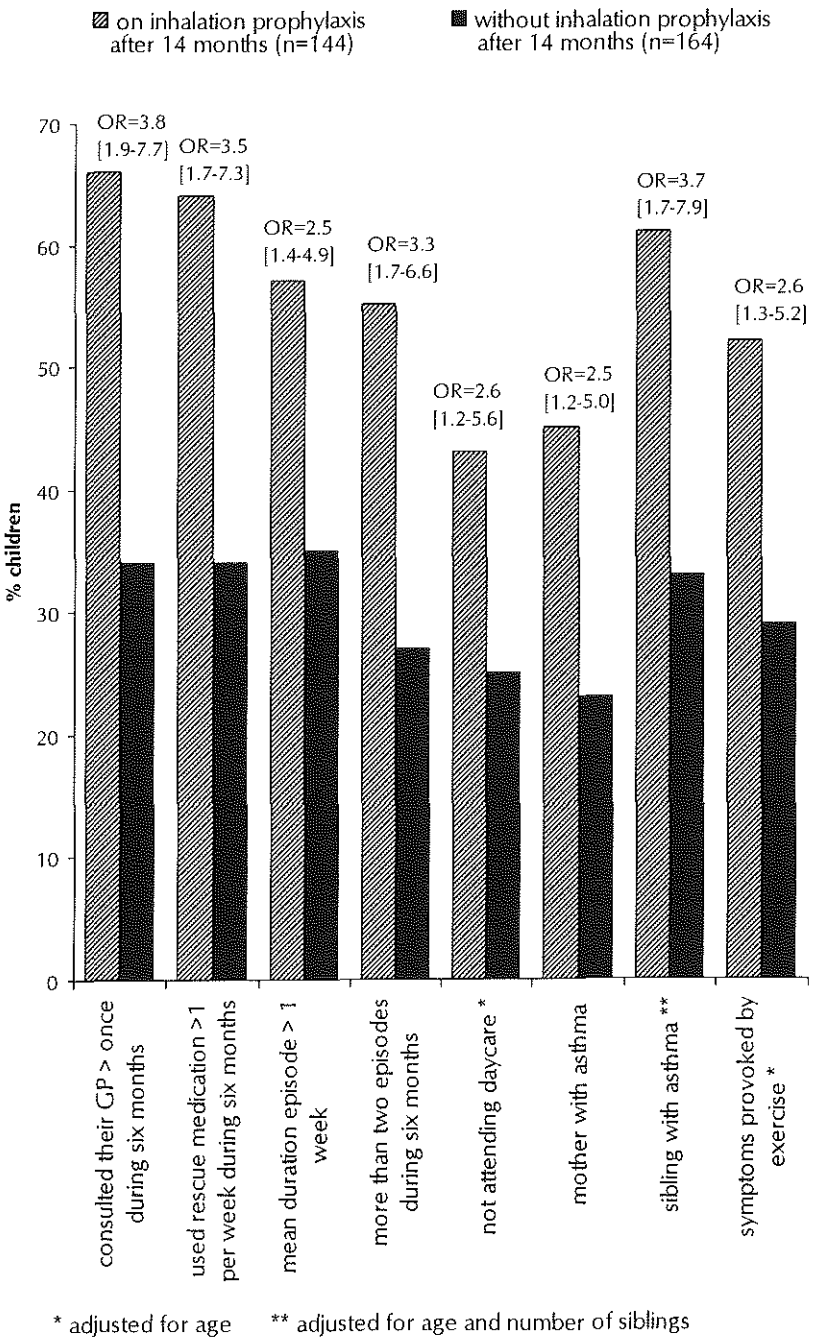

Figure 1
Determinants of long-term used of inhaled prophylaxis in preschool children with moderate asthma

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Inhaled sodium cromoglycate in children with asthma: a systematic review

We thank Fisons plc, Loughborough, UK for searching their database for clinical trials and S.M.A. Bierma-Zeinstra for scoring our trial.

Introduction

Several guidelines for the management of childhood asthma have been published by international consensus groups, recommending early preventive treatment to reduce the need for bronchodilators and to enable asthmatic children to lead a normal and active life.[1,2] The consensus statements recommend sodium cromoglycate (SCG) as maintenance treatment of children with moderate asthma. SCG is supposed to be effective in 60% of the cases,[3] but predictors of success are not known. Although SCG has been used for decades, the precise mechanism of action is still not fully understood. No serious side-effects have been reported in trials, but dysuria, urticaria, bronchospasm, angio-oedema and anaphylaxis can occur.[4,5,6]

In a recently published review and position statement of the British Asthma Co-ordinating Committee, SCG and corticosteroids were both posited as first choice preventive therapy in young children, rather than recommending use of SCG as first choice before inhaled corticosteroids;[7] the grounds for this decision are, however, still unclear. The long-term side effects of preventive asthma treatment with inhaled steroids in early childhood are unknown. Nevertheless, there is concern that treating very mild cases of asthma with inhaled steroids may have an adverse effect on the balance between risk and benefit; therefore sodium cromoglycate may still be considered as first choice preventive treatment.[7] Other recent guidelines continue to recommend SCG as first choice in young children.[8]

The use of SCG has decreased since 1990, while the use of inhaled corticosteroids is increasing (even in young children).[9,10] Nowadays, few consultant paediatricians use cromoglycate as first-line treatment in young children,[11] whereas some studies suggest overtreatment of children with mild asthma with inhaled corticosteroids.[9,12]

The discrepancy between guidelines and daily practice, and the debate on the role of SCG, which led to its recent withdrawal as first line treatment in young children, was the rationale to review the effectiveness of SCG in the treatment of childhood asthma. We systematically reviewed all published randomised placebo-controlled trials of SCG in the prophylactic treatment of asthma in children. The aim of the study was to assess the methodological quality of the studies and the effectiveness of inhaled sodium cromoglycate by statistical pooling of the study results.

Methods

Selection of studies

Literature searches of Medline, Embase, the Cochrane Controlled Trial Register[13] and the database of the pharmaceutical company manufacturing SCG were carried out for the period January 1966 to December 1997. The MESH-keywords [asthma], [sodium cromoglycate] and [clinical trial] were used to identify relevant articles. After the search we reviewed the reference lists of all relevant articles and all double-blind placebo-controlled, randomised clinical trials were selected which included children aged 0-18 years old, which addressed maintenance therapy, and were published in English.

Methodological assessment

All trials were scored according to the criteria listed in Table 1 and Appendix 1. The scoring method was based on the well-known principles for assessing the quality of intervention research.[14] For a number of criteria a weighting system was used, giving a maximum score of 95 points for a study.[15] Table 1 shows the eight categories into which the items were arranged. We decided that the items 'proper retrospective analysis' and 'multiple looks considered' from the original scoring list were not applicable because these procedures are uncommon in studies addressing prophylactic asthma therapy. In crossover studies we considered the presentation of prerandomisation characteristics to be less important than in parallel studies, thus the maximum score in crossover studies was 94 instead of 95.

Table 1
Criteria for the methodological assessment of randomised controlled trials
(For details, see Appendix 1.)

Criterion		Weight
A	Selection and inclusion	6
B	Randomisation procedure	13
C	Blinding	23
D	Intervention	6
E	Withdrawals	7
F	Compliance	6
G	Statistics and analysis	24
H	Presentation of results	10
Total		**95**

The methodological quality of the studies was assessed independently by two (MJAT, JHJMU) of the three reviewers, two general practitioners and a methodologist. Before scoring the trials the reviewers mutually adjusted their interpretation of the items. The results were discussed in a consensus meeting; in case of lack of consensus the assessment of the third reviewer (JCvdW) determined the final decision. To avoid "reviewers' review bias" our own trial[16] was also scored by an impartial reviewer (SMA Bierma-Zeinstra).

Outcome of the studies

The general outcome of each study was derived from the conclusions drawn by the authors. A study was judged positive when the authors concluded that cromoglycate was more effective than placebo. A study was classified as "equal" when the authors reported no difference between the treatments. No studies in favour of placebo treatment were found. The methods and conclusions of the different trials were summarized and tabulated.

Statistical pooling

For each study the 95% confidence interval (CI) for the difference in symptom score between placebo and cromoglycate treatment was calculated, separately for "wheeze" and "cough". If no separate scores were available we used the score for "daily symptoms". In case the published data were not sufficient to compute a 95% CI and the trial was published not more than 5 years ago, we sent a request for data to the authors. If, apart from the statement "not significant", no exact p-value was given we calculated the effect of two extreme alternatives (p=0.10 and p=0.90). Most studies used a scale of 0-3 points; in case a different scale was used it was transformed for our purposes. We computed the pooled estimates of the treatment effect and the pooled 95% CI and tested the hypothesis of homogeneity.[17] In case of heterogeneity the pooled confidence interval was computed taking heterogeneity into account[17] and the corresponding tolerance interval.[18] In order to explain heterogeneity the influence of study characteristics on the outcome was evaluated by means of univariate and multivariate regression analysis (observations weighted by the reciprocal of the square of the standard error of the mean difference between placebo and SCG). The influence of asthma severity of the study population (expressed in the mean placebo score) on the outcome was evaluated by means of functional relationships.[19] To further explore heterogeneity a funnel plot was made of the effect estimate against the precision[20], for all trials. The precision of a trial was defined as 1/standard error. The symmetry of the funnel plot was tested.[21]

To show the relative difference in treatment effect, for each study the relative improvement in mean (RIM) (= percentage improvement compared to placebo) was calculated:[22]

RIM = [mean score [placebo] - mean score [SCG]] * 100 / mean score [placebo]

A similar pooling and testing for homogeneity, as described above, was performed; for this procedure a first order approximation was used as an estimate of the standard error of the RIM.

Results

Studies

A total of 251 articles was identified in Medline of which 17 met our inclusion criteria.[23-39] Embase provided one additional trial[16] and two additional trials were provided by the database of the pharmaceutical company.[40,41] The Cochrane Controlled Trial Register did not supply further trials, but two more trials were found by searching the references of relevant articles.[42,43] The excluded studies were either not double-blind, not randomised, not controlled, did not concern the appropriate age group, or investigated the effectiveness of SCG on exercise-induced asthma; one double blind cross-over study was excluded because the results were only partially presented.[44] Finally, 22 randomised controlled trials (RCTs) of SCG as prophylactic agent in children with asthma were reviewed. The characteristics of the included trials are presented in Table 2; the studies were European (n=15, of which 9 were British) and North American (n=7). Studies differed in design, severity of asthma, number of children included, age of children, administration of medication, follow-up period, and year of publication. In total, 900 children were studied in the 22 trials, with sample size ranging from 9 to 218 children; 480 children (11 trials) were of preschool age and 420 were 5 years or older (11 trials). Prior to 1977, studies included only children aged 5 years and over. The median duration of intervention was 4 weeks (range: 3 - 26 weeks). All studies included children with moderate to severe asthma, and all but one study were hospital-based. In nine papers it was unclear whether the population was hospitalised or ambulatory, nor was it clear whether and what concurrent medication was permitted during the trial.[24,26,31,34,36,38-40] Only one trial selected children with moderate asthma through general practitioners.[16] Compliance was discussed in only four papers.[16,23,24,28]

Side-effects

Thirteen RCTs reported side effects, all these were minor and the incidence was low. Cough was most often reported, followed by bitter taste, wheeze, sneeze, throat irritation and perioral eczema. Some studies did not specify the kind of adverse effects but merely stated 'minor'.

Outcome

In 15 studies a positive outcome was concluded, and 2 studies were partially positive, depending on age[26] and symptom.[39] Five RCTs had an equal outcome. We disagreed with the positive conclusion of three of the studies. First, the conclusion by Fox and colleagues[34] that SCG is beneficial was based on three assessments (clinical assessment, (parental) symptom score and FEV_1). All three assessments were available in only 22 children of the 28 children included in the

Table 2
Randomised controlled trials evaluating the effectiveness of inhaled sodium cromoglycate (SCG) in children

Reference	Setting	Design	Dose SCG	Additio-nal study arm	Inclusion criteria	Age (yrs)	No. of patients included/ analysed	Duration intervention period(s)	Major effect parameters	Side effects	Authors' conclusion	Review score
Smith et al.[41] (1968)	school health service	cross-over	4 dd 20 mg Spinhaler	none	Longstanding perennial asthma	5-16	51/44	2x4 weeks	daily symptom scores lungfunction additional medication laboratory	cough	positive	44/91 (0.48)
Hyde et al.[38] (1970)	not specified	cross-over	4 dd 20 mg Spinhaler	none	duration of asthma > 1 year definite symptoms before inclusion	6-16	60/57	2 x 3 weeks	daily symptom scores clinical assessment lung function additional treatment	irritated throat, headache, cough, wheeze	positive	43/91 (0.47)
Sly [39] (1970)	outpatients	cross-over	4 dd 20 mg Spinhaler	none	asthmatic, responded on exercise with bronchospasm	6-12	21/16	2 x 4 weeks	daily symptom scores clinical assessment lung function lab tests, X-ray, additional treatment	sore throat	positive/ equal	38/94 (0.40)
Collins et al.[36] (1971)	out- and inpatients	cross-over	4 dd 20 mg Turbuhaler	none	severe allergic asthma, wheezed at least once a week	7-17	63/63	2 x 4 weeks	daily symptom scores clinical assessment lung function	cough, dry mouth, dizziness nausea, headache	positive	39/94 (0.41)
Limburg [37] (1971)	inpatients	cross-over	4 dd 20 mg Spinhaler	none	in asthma centre and regular asthma symptoms	6-16	30/29	2 x 4 weeks	daily symptom scores lung function additional treatment	cough	positive	45/94 (0.48)
Fox et al.[34] (1972)	hospital	cross-over	4 dd 20 mg Spinhaler	none	chronic severe perennial bronchial asthma, a period of observation in the clinic for at least one year and pulmonary function impairment	5-16	23	2 x12 weeks: treatment	daily symptom scores, clinical assessent, lung function	cough	positive	32/91 (0.35)

Table 2 – continued

Reference	Setting	Design	Dose SCG	Additio-nal study arm	Inclusion criteria	Age (yrs)	No. of patients included/ analysed	Duration intervention period(s)	Major effect parameters	Side effects	Authors' conclusion	Review score
Silverman et al.[35] (1972)	outpatients	parallel	4 dd 20 mg capsules	none	perennial asthma and disability exceeding 6-8 wks in preceding year, or 3-4 wks in preceding 3 months despite of regular bronchodilator therapy, never use of corticosteroids or cromoglycate	7-9	53	2 weeks: baseline 8 weeks: treatment	daily symptom scores, clinical assesment, lung function	cough, dry throat	positive	39/92 (0.42)
Hyde et al.[33] (1973)	hospital	cross-over	4 dd 20 mg Spinhaler	none	chronic disabling asthma	5-16	38	4 weeks: baseline 2x4 weeks: treatment	additional treatment, clinical assessent, lung function	cough, throat pain, dizzy	positive	38/87 (0.44)
Crisp et al.[32] (1974)	unspecified	cross-over	4 dd 20 mg small device	none	chronic asthma and 2 out of: nearly daily symptoms; nearly daily medication needed; intermittent or long term steroid usage	5-17	40/40	2 x 4 weeks	daily symptom scores clinical assessment lung function additional medication	rash, wheeze	positive	45/87 (0.52)
Hiller et al.[31] (1975)	unspeciefied	cross-over factorial	4 dd 20 mg Spinhaler	beta-metha-sone 17 valerate	chronic perennial asthma, symptoms inadequately controlled by scg and bronchodilators	9-13	11/9	4 x 1 month	daily symptom score clinical assessment additional medication	none	positive	44/87 (0.51)
Hiller et al.[29] (1977)	hospital	cross-over	3 dd 20 mg nebulised	none	frequent troublesome asthma	2-4	17	1 week: baseline 2x4 weeks: treatment	daily symptom scores, clinical assessent, lung function	unspecified	positive	34/87 (0.39)
Matthew [30] (1977)	outpatients	cross-over	4 dd 20 mg nebulised	none	severe chronic perennial asthma + symptoms in baseline period	3-6	9	8 weeks: baseline 2x4 weeks: treatment	daily symptom scores, additional treatment, lung function	unspecified	positive	29/87 (0.33)

Edmunds et al.[28] (1980)	unspecified	cross-over	4 dd 1 capsule	slow-release amino-phylline	perennial asthma	5-15	30/30	3 x 4 weeks	daily symptom scores, lung function, additional medication	nausea, vomiting, abd. pain, headache	positive	29/91 (0.33)
Glass et al.[27] (1981)	hospital	cross-over	4 dd 20 mg nebulised	Theo-phylline syrup 4 dd, to body weight	control of asthma was poor under routine treatment	1-4	16	4 weeks: baseline 3x8 weeks: treatment	daily symptom scores, additional treatment	minor	equal	29/94 (0.31)
Geller-Bernstein et al.[26] (1982)	hospital	cross-over	4 dd 2 ml nebulised	none	frequent troublesome wheezy bronchitis despite regular bronchodilator therapy + symptoms in baseline period	0-2	44	2 weeks: baseline 2x4 weeks: treatment	daily symptom scores, clinical assessent	unspecified	equal/ positive	34/94 (0.36)
Miraglia del Giudice et al.[40] (1982)	hospital	cross-over	3 dd 20 mg nebulised	none	perennial asthma and symptoms despite bronchodilator therapy	0-5	31	2 weeks: baseline 2x4 weeks: treatment	daily symptom scores, additional treatment, clinical assesment	cough, sneeze	positive	35/91 (0.38)
Henry et al.[25] (1984)	hospital	cross-over	3 dd 20 mg nebulised	ipratro-pium bromide 3 dd 250lg	suffered from recurrent attacks of wheezing and considered troublesome asthma by pediatrician and parents	<2	20	2 weeks: baseline 3x8 weeks: treatment	daily symptom scores, additional treatment, lung function	unspecified	equal	23/94 (0.24)
Cogswell et al.[24] (1985)	hospital	cross-over	4 dd 20 mg nebulised	none	regular attacks of asthma that required at least one admission to hospital	1-4	24	4 weeks: baseline 2x26 weeks: treatment	daily symptom scores, additional treatment	unspecified	positive	43/91 (0.47)
Bertelsen et al.[43] (1986)	hospital	parallel	3 dd 20 mg nebulised	none	recurrent wheezy bronchitis demanding therapy at least once a month during preceding winter or later	1-4	54	4-8 weeks: baseline 10 weeks: treatment	daily symptom scores, additional treatment	cough,wheeze and eczema	equal	31/95 (0.33)

Table 2 – continued

Reference	Setting	Design	Dose SCG	Additio-nal study arm	Inclusion criteria	Age (yrs)	No. of patients included/ analysed	Duration intervention period(s)	Major effect parameters	Side effects	Authors' conclusion	Review score
Yuksel et al.[42] (1992)	hospital	cross-over	4 dd 5 mg coffeecup	none	preterm born, wheeze and/or cough 3-4 days/week for the previous 4 weeks + sypmtoms for at least 3 days following all respiratory tract infections	0-2	16	2-3 weeks: treatment	daily symptom scores, additional treatment, lung function	unspecified	positive	32/91 (0.35)
Furfaro et al.[23] (1994)	outpatients	parallel	3 dd 40 mg nebulised	none	presence of chronic pulmonary symptoms for at least one month and wheezing documented by a physician + symptoms in baseline period	0-1	31	3 weeks: baseline 6 weeks: treatment	daily symptom scores, lung function	unspecified	equal	56/95 (0.59)
Tasche et al.[16] (1997)	general practice setting	parallel	3 dd 10 mg Spacer-device + facemask	none	previously been prescribed anti-asthma medication and meeting formulated criteria for moderate asthma	1-4	218	4 weeks: baseline 22 weeks: treatment	daily symptom scores, loss of participants, additional medication	eczema in mask area, cough	equal	75/95 (0.79)

study. They consider it of practical importance that 14 children showed improvement based on at least one of the assessments; we question this positive conclusion. The second study in which we disagreed with the authors was the crossover study by Hiller et al.[29] Their conclusion that SCG was beneficial in 11 of 17 children was based on the opinion of the parents. Symptom scores for cough changed significantly in favour of the SCG group, symptom scores for wheeze did not. Four children required one or more short courses of steroids during the follow-up period of four weeks. Moreover, it is unclear during which type of treatment the rescue medication was given. Finally, Collins-Williams et al.[36] found a significant improvement after SCG treatment in (only) four out of nine symptoms, yet concluded that the treatment was useful.

Methodological assessment

The results of the methodological assessment are given in Table 3; the decision of the third reviewer was necessary for one article.[34] The methodological scores ranged from 24% - 79%; the mean score of 43% indicated mediocre methodology. The most prevalent methodological shortcomings were in the areas of compliance (a mean of only 8% of the maximum attainable score on this item for all studies), selection and inclusion (23%) and statistics and analysis (28%). The mean scores for the description of blinding and intervention were relatively good; 66% and 64% respectively; however, the ranges of these proportions are large. Twelve studies were published before 1980. The mean method score for these latter studies was 43% (range 33-52%) versus 42% (range 24-79%) for the 10 trials reported after 1980. Our own recent study scored highest; to control for reviewers'-review bias, the independent observer re-evaluated our study, which resulted in similar scores.

Statistical pooling

For most studies the data were insufficient to allow a formal meta-analysis with odds ratios. Figure 1 presents two graphs of 95% CIs of differences in mean symptom score (placebo minus SCG) for each study. The CIs are ordered according to year of publication of the study. In seven studies the CIs were calculated using the separate symptom score of "wheeze" and "cough", in 11 studies we used "day symptoms". In two studies[36,39] only the results for "cough" were presented; data on "wheeze" were not published because the difference in treatment effect between placebo and SCG was not significant.

The chi-square test rejected the hypothesis of homogeneity of the study results ($p<0.005$), both for the absolute and the relative outcome measures. This heterogeneity could be due to the year of publication of the trial, the study design (parallel/cross-over), age of the children, placebo symptom level (i.e. severity of asthma), method of administration of the medication, duration of follow-up, fre-

Table 3
Methodological quality of RCTs evaluating the effectiveness of inhaled sodium cromoglycate in children.

Reference		A	B	C	D	E	F	G	H	method score*	method score %	authors' conclusion
maximum score		**6**	**13**	**23**	**6**	**7**	**6**	**24**	**10**	**95**		
Smith et al.[41] (1968)		1	4	19	6	3	1	8	2	44/91	48	positive
Hyde et al.[38] (1970)		1	4	20	6	2	0	4	6	43/91	47	positive
Sly [39] (1970)		0	4	13	5	3	0	7	6	38/94	40	positive/equal
Collins et al.[36] (1971)		2	7	18	6	0	0	3	3	39/94	41	positive
Limburg [37] (1971)		1	4	13	5	3	0	11	8	45/94	48	positive
Fox et al.[34] (1972)		1	5	14	6	0	0	2	5	32/91	35	positive
Silverman et al.[35] (1972)		3	7	16	1	1	0	8	3	39/92	42	positive
Hyde et al.[33] (1973)		1	6	13	4	3	0	6	5	38/87	44	positive
Crisp et al.[32] (1974)		3	6	17	6	3	0	8	2	45/87	52	positive
Hiller et al.[31] (1975)		2	10	18	4	3	0	5	2	44/87	51	positive
Hiller et al.[29] (1977)		0	10	14	4	3	0	2	1	34/87	39	positive
Matthew [30] (1977)		0	4	13	4	3	0	3	2	29/87	33	positive
Edmunds et al.[28] (1980)		0	4	14	0	1	2	6	2	29/91	33	positive
Glass et al.[27] (1981)		0	4	14	2	0	1	6	2	29/94	31	equal
Geller-Bernstein et al.[26] (1982)		1	4	16	2	3	0	6	2	34/94	36	positive/equal
Miraglia del Giudice et al.[40] (1982)		1	4	14	3	3	0	7	3	35/91	38	positive
Henry et al.[25] (1984)		0	0	16	3	0	0	2	2	23/94	24	equal
Cogswell et al. [24] (1985)		1	10	13	4	3	1	9	2	43/91	47	positive
Bertelsen et al.[43] (1986)		1	3	12	3	3	0	6	3	31/95	33	equal
Yuksel et al.[42] (1992)		3	4	13	3	1	0	5	3	32/91	35	positive
Furfaro et al.[23] (1994)		3	13	13	5	4	3	11	4	56/95	59	equal
Tasche et al.[16] (1997)		6	11	20	3	6	3	21	5	75/95	79	equal
percent score per item	mean	23	45	66	64	33	8	28	35		43	
	range	0-100	0-100	52-87	0-100	0-86	0-50	8-88	10-80		24-79	

* Denominator reduced for crossover studies and for nonapplicable items (see text)

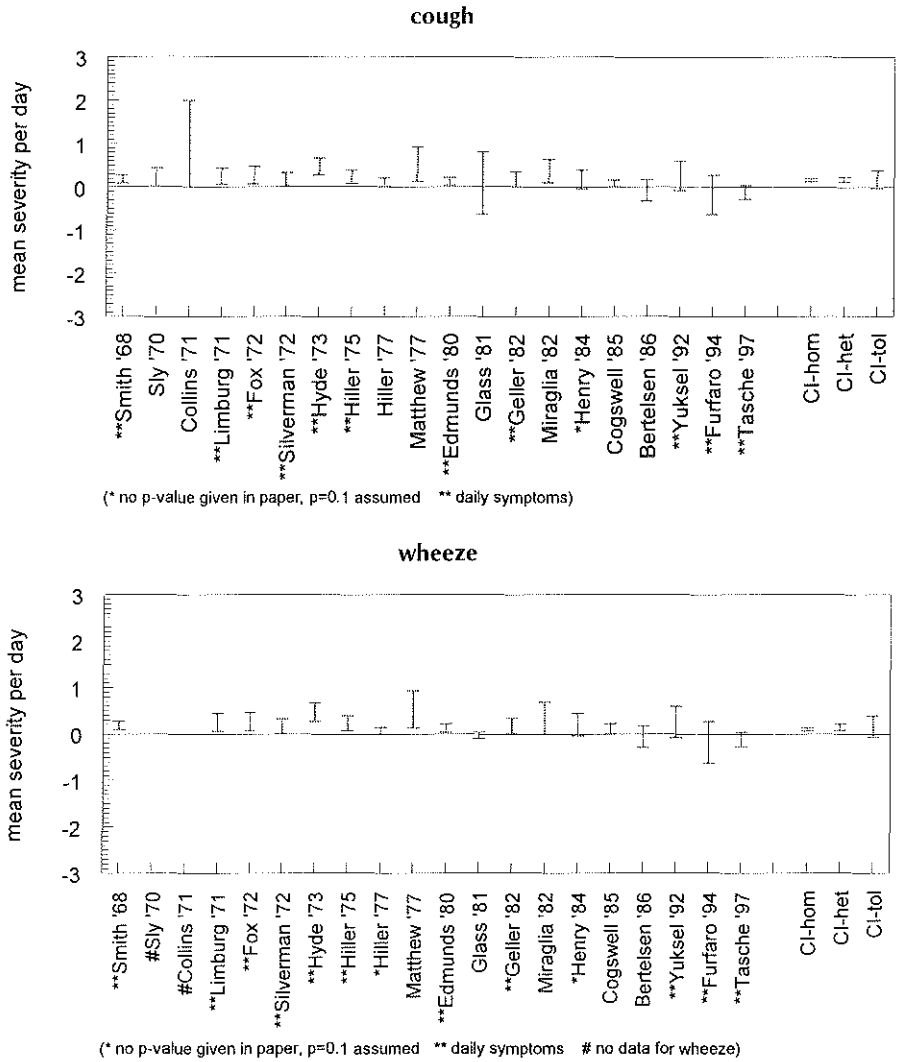

Figure 1
95% confidence intervals of absolute difference for symptoms

quency of dosage, methodological score, and other study characteristics. Only year of publication, age of the children, and study design were significant predictors of outcome in the univariate regression analysis. The multivariate regression analysis showed that only year of publication and study design were significant predictors of the effect size: older cross-over studies were more likely to produce a positive effect of SCG treatment. Age of the children, which was highly correlated with year of publication (ρ=0.83), was not significant in this analysis. There

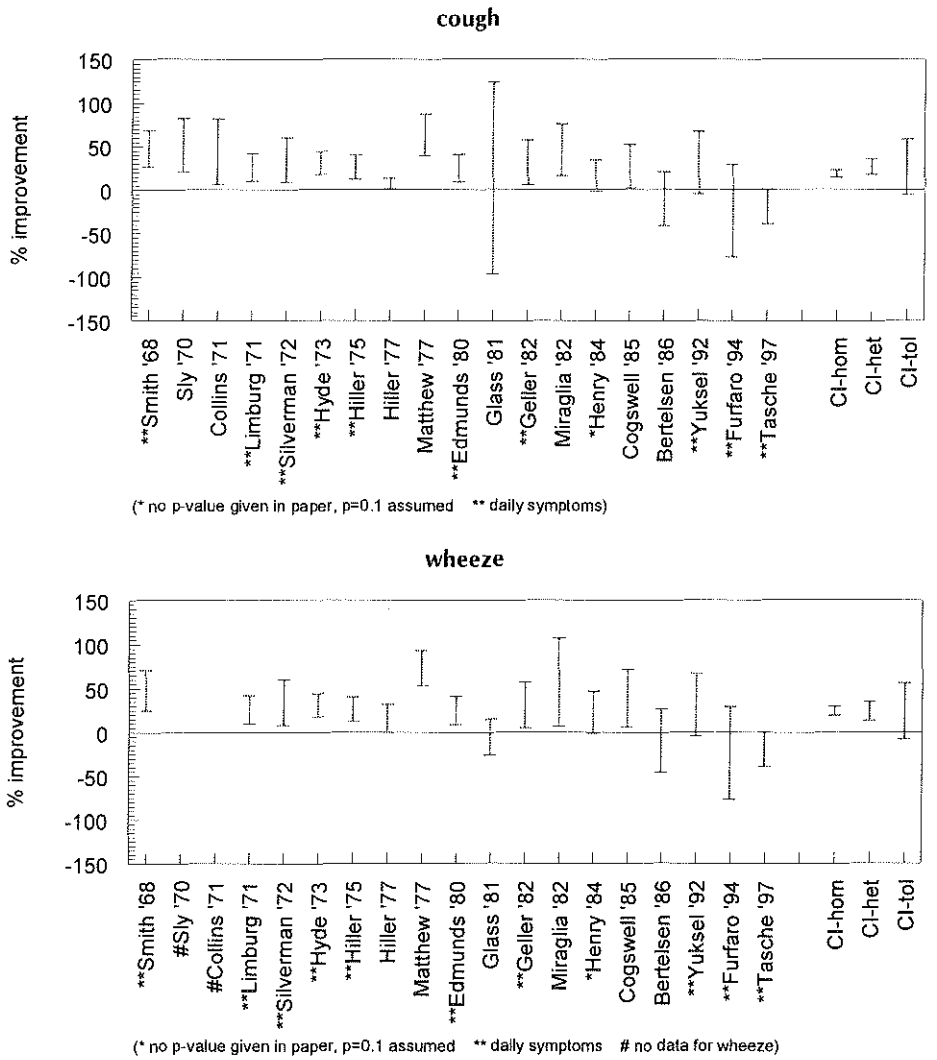

Figure 2
95% confidence intervals of relative difference for symptoms.

was a linear relation between treatment effect and control level (slope 0.96 (SE:0.08); intercept -0.13 (SE:0.05). The conclusion of this analysis is that heterogeneity cannot be explained by asthma severity, and transformation of the data into RIM does not change the conclusion of heterogeneity.

The pooled 95% CIs under the assumption of heterogeneity and the corresponding tolerance interval are shown in Figures 1 and 2. The latter includes zero, both

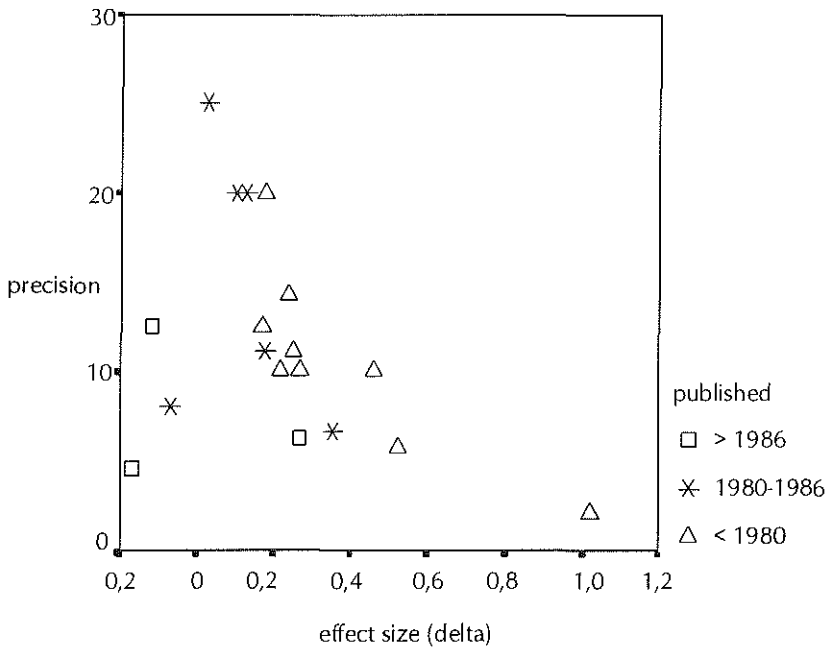

Figure 3
Funnel plot for effect size (delta) versus precision (1/standard error) of selected trials.

for the absolute treatment effect and for the relative treatment effect. The funnel plot is shown in Figure 3; the hypothesis of symmetry was rejected (p=0.028). The asymmetric funnel shows that small studies with negative or equal outcomes are underrepresented.

Discussion

This review shows that no firm conclusions can be drawn on the therapeutic effect of SCG compared to placebo. In the statistical pooling of the trial results we computed the 95% CI assuming heterogeneity and the 95% tolerance interval because the test on homogeneity was rejected. The latter interval included zero, indicating that the outcome of future studies cannot be predicted.[18]

Study characteristics

Although SCG was indicated as treatment for mild to moderate asthma, nearly all trials comprised hospital-based populations of children with moderate to severe asthma. Nine studies administered the medication by nebulisation. Nowadays, spacer devices are available for young children, which are less time-consuming and less tedious than nebulisers, particularly at home. Metered dose inhalers with

spacer devices were used in only two studies.[16,42] Spinhalers were used in 11 trials with older children. The way of administration, a critical factor in dose delivered to the lungs, was not a predictor of outcome. Diagnosis and measurement of asthma in young children is difficult[45,46] and age effects might reduce or mask the effects of sodium cromoglycate. However, this is unlikely: although children's age was a significant predictor for treatment effect in the univariate analysis, the multivariate analysis showed that publication date of the trial was a confounder for age of the children. Follow-up duration in 14 trials did not exceed 4 weeks, which, according to guidelines, may be too short to assess treatment effect. Although duration of follow-up was not a predictor of outcome, it was notable that none of these short-term trials had an 'equal' conclusion (12 were positive and 2 were positive/equal). In 7 studies the authors tried to find characteristics or criteria to predict which children would respond to cromoglycate; however, none were found[16,24,25,34,35,37,43] Silverman et al.[35] reported that only the acute protective effect of SCG in exercise tests predicted the probable success or failure of long-term treatment with the drug.

Earlier reviews

The effects of treatment with SCG have been reviewed earlier. Edwards[47] examined the evidence for the anti-inflammatory action of cromoglycate in adults and children; he discussed a large number of controlled and uncontrolled studies but it is unclear how these were selected. Hoag and McFadden[48] summarized studies on the effect of cromoglycate on bronchial hyperreactivity in adults and children. The review by Schweitzer and Brossier Ballano[49] discussed three controlled studies assessing the efficacy of cromoglycate in children aged 2 years and younger. Finally, Holgate[50] reviewed recent trials with metered dose inhalers in children and adults and discussed challenge studies, therapeutic studies and long term effects of SCG. None of the earlier reviews were systematic, assessed the methodologic quality or tried to quantify treatment effects.

Methodological assessment

Meta-analysis and scores related to drug therapy have been criticised, but are increasingly popular, because they give insight in the combined results of trials and provide data for rational decision making.[51,52] A review of scales and checklists for assessing the quality of randomised controlled trials shows limitations in virtually every scale.[14] We decided to use the items proposed by Chalmers[15] because they address the methodology and the presentation of the study extensively. However, we found shortcomings while using the scale, including the lack of attention for sample size, protocol violations and permitted concurrent medication.

The methodological quality of the RCTs reviewed here was poor, as demonstrated by the mean score of 43% of the maximum attainable score. We have to take into account that 12 studies were published prior to 1980; informed consent, clear description of inclusion criteria, rejection logs and baseline characteristics, adequate sample size calculation, calculation of confidence intervals, and regression analysis were not common practice at that time.

Statistical pooling

The estimates of the differences between placebo treatment and cromoglycate treatment for symptom scores of "cough" and "wheeze" (under assumption of homogeneity) were 0.16 and 0.10, respectively. This is suggestive of a small therapeutic effect of cromoglycate. We doubt whether this is of clinical relevance. On the other hand, the overall relative improvement estimates were 18% and 24%, respectively. This high relative improvement combined with the minor absolute improvement shows that, overall, the severity of symptoms under placebo treatment was low. Indeed, although most studies in our review included children with severe asthma, the mean daily symptom score in the placebo groups was low (0.8). This is mainly due to a dilution by symptom free days, a common finding in trials of childhood asthma.[53,54]

One should be cautious about drawing definitive conclusions concerning the role of sodium cromoglycate in the treatment of asthma in children on the basis of this review for several reasons. Medical literature can be misleading as a result of selective submission and publication of RCTs showing a statistically significant treatment effect.[55] Year of publication of the study proved to be the most significant predictor of treatment effect and the asymmetric shape of the funnel plot suggests bias: studies with a positive treatment effect had relatively little precision and most were performed before 1980. An explanation might be that attention for publication bias started around 1980.[55,56] The trials were heterogeneous in their treatment effects. Refraining from pooling has been a serious option considering the heterogeneity and the publication bias.[57] Nevertheless, we calculated the pooled confidence intervals and the tolerance interval as useful summary measures. In two trials[36,39] the results for "wheeze" were not published because the difference between placebo and cromoglycate was not significant. This could result in some bias in favour of SCG in the "wheeze" calculation. On the other hand, two trials[32,33] with positive outcomes were omitted from the pooling because the published data were insufficient. The results of the statistical pooling were based on symptoms only, because symptom scores were available in all trials. We did not include studies on the immediate effects of SCG on exercise-induced asthma. This is a different issue, not pertaining to the use of SCG as advised by current guidelines. Finally, we did not include studies on the effects of combined therapy, i.e. the corticosteroid-sparing effects of cromoglycate.

Conclusion

We conclude that, on the basis of published randomised trials, the superiority of SCG over placebo in the maintenance treatment of asthmatic children has not been proven. Therefore, we consider it is justified to recommend SCG no longer as a first-line prophylactic agent in childhood asthma.

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Appendix 1

Operationalisation of the criteria for methodological assessment of randomised controlled trials according to Chalmers [15]

A Selection description (3 points). Number of patients seen and reject log (3 points).

B Randomisation blinding, method of random blinding (10 points). Testing randomization (3 points).

C Blinding of patients (8 points). Blinding of physicians re therapy (8 points). Blinding of physicians and patients re results (4 points), testing blinding (3 points).

D Therapeutic regimens definition (3 points). Control regimen (placebo) appearance (1.5 points). Control regimen taste (1.5 points).

E List of withdrawals (3 points). Handling of withdrawals in analysis (4 points).

F Testing compliance (3 points). Biological equivalent (3 points).

G Prior estimates of numbers (endpoints selected, difference of clinic interest α and β estimated) (3 points). Test statistic and observed probability value are stated (3 points). Posterior β estimates of observed difference for negative trials mentioned (3 points). Confidence limits (2 points). Life-table or time series analysis shown (2 points). Regression analysis correlation (2 points). Appropriate statistical analysis (4 points). Statistical discussion side effects (3 points). Blinding statistician or analyst re results (2 points).

H Dates of starting and stopping accession (2 points). Results of pre-randomisation: data analysis, prognostic favouring (2 points, in crossover studies 1 point). Tabulation of events employed as endpoint for each treatment (2 points). Timing of events (4 points).

Discussion, conclusions and suggestions for further research

The main aim of this thesis was to investigate the feasibility of long-term inhalation therapy and the effectiveness of sodium cromoglycate, in young children in a general practice setting. To achieve this aim we conducted a small study of searching strategies in the computerised files of general practitioners, a randomised placebo-controlled trial in primary care and a systematic review on sodium cromoglycate. The feasibility of inhalation therapy was further discussed in a separate chapter, and a follow-up study eight months after finishing the trial was done. We now discuss the major findings along the lines of the research questions formulated in chapter one, and give suggestions for further research.

Feasibility of prophylactic inhalation therapy in young children

In our five-month study (chapter three), patient compliance was relatively high, even with an intensive daily regimen and a drug that turned out to be not more effective than placebo. Compliance was probably high because of the home-based trial setting and our intensive monitoring through home visits. It is a well-known fact that compliance in daily practice will always be lower than in a closely supervised trial situation. Moreover, in the recruitment phase prior to the inclusion a selection of children and parents had taken place; parents who foresaw feasibility problems did not start the trial. Although our findings show that in young children long-term inhalation treatment is feasible in the home situation, physicians should be aware that a considerable proportion of the parents are reluctant to start, or will discontinue, long-term prophylactic inhalation therapy. Compliance of prophylactic treatment showed a relation with current symptoms (chapter five), suggesting that parents of young children with moderate asthma who are confronted with their child's symptoms will become more compliant in administering prophylactic medication to their child. Timely, intermittent short treatment with anti-inflammatory drugs for episodes of moderate asthma in young children might possibly be beneficial and more feasible. Wilson and Silverman investigated the effects of high-dose inhaled steroids at home for acute, episodic asthma in preschool children recruited from a hospital population.[1] They concluded that this treatment was beneficial in modifying the severity of the attacks, although the results were influenced by hospital admission and oral corticosteroid treatment. This kind of application might be promising and has so far never been investigated in young children with mild and moderate asthmatic symptoms in general practice.

In national and international guidelines, inhalation therapy is recommended as the preferred way to administer anti-asthmatic drugs to young children.[2,3] Oral anti-asthmatic drugs are often prescribed for children who might be able to use an inhaler effectively.[4,5] Many physicians and/or parents apparently still prefer

non-inhalation therapy in this young age group. Therefore, it is very interesting to explore the effectivity, safety and compliance of anti-asthma drugs that can be given by means other than inhalation. The first and most accepted route is the oral one. The first candidate for this route of administration are the oral anti-leukotrienes that seems worthwhile to investigate in this age group.[6] Second, oral salbutamol versus inhaled salbutamol in transient episodes of wheezing in young children has never been investigated in general practice. Third, deptropine, an anti-cholinergic, is often prescribed in the Netherlands for young children with asthmatic symptoms,[5] but has not been studied in a trial comparing the drug with placebo or an alternative drug. A second route of administration might be nasal; nasal administration of anti-inflammatory drugs rarely has been investigated for their effects on asthma. When given for rhinitis, they often show beneficial effects on respiratory symptoms in preschool[7], school-age children[8], and adults[9], but this has not yet been demonstrated in a clinical trial focussing on children with asthma.

For symptom relief, without prophylactic aims, short-acting bronchodilators are recommended. Long-acting beta-mimetics are not indicated for this purpose, mainly because of the fear of masking symptoms, thus introducing a risk for delay in starting anti-inflammatory prophylactic treatment. Now that we are aware of this risk, preschool children with mild and moderate asthma can perhaps be adequately treated with long-acting bronchodilators. It might be sensible to explore this theory in a properly designed trial.

Effects of inhalation therapy with sodium cromoglycate

In national and international guidelines prophylactic therapy is recommended in an early stage of the disease.[2,3] Recently, sodium cromoglycate and inhaled steroids were both advocated as drugs of first choice for preventive treatment of moderate asthma, rather than recommending use of cromoglycate before inhaled steroids. Until our study, the effectiveness of cromoglycate was never investigated in a placebo-controlled trial in young children with moderate asthma in general practice. In addition to such a trial, we performed a systematic review of clinical trials with sodium cromoglycate published up to 1998.

In our trial, children in both the cromoglycate group and the placebo group improved significantly during the trial period. This finding could be explained by a placebo effect, natural course of the disease and the personal supervision associated with a clinical trial, as found previously in many trials on asthma in children. No differences in any outcome measure were found and no serious side effects were reported for either of the groups by parents or general practitioners.

Our trial showed no benefit of sodium cromoglycate. Several explanations can be addressed that might explain the negative finding, namely: the selection of children with (moderate) asthma, the dose of cromoglycate prescribed, the spacer device with face-mask and drug delivery to the lungs, subjective symptoms as outcome measure, the length of follow-up and the statistical power of the trial. Each item will be discussed.

Moderate asthma

It is possible that we selected children with asthma as well as children with transient wheezing. The uncertainty of labelling recurrent and chronic respiratory symptoms in young children as 'asthma' is discussed in chapter one. It is difficult to distinguish between 'asthma' and 'wheezing' in preschool children, hence these are combined under the label 'asthma' in this age group. Since cromoglycate is recommended for mild and moderate asthma and these children are mainly treated by their general practitioner[10], we selected children from general practices to investigate appropriate patients. The severity of asthma was classified according to current guidelines, based on symptoms and medication used, because objective outcome measures are not available in the home situation. The children classified as having moderate asthma had a prescription of an anti-asthma drug in the past, and had actual symptoms and/or medication. The children on maintenance treatment with inhaled steroids were classified as having severe asthma and were therefore excluded. The children with moderate asthma who started the trial had symptoms on 48% of the days in the baseline period, hence preventive treatment was indicated. If the therapeutic effect of sodium cromoglycate in our trial had been diluted by transient wheezers (non-asthmatics), we would have expected to find some influence of patient characteristics like atopy, parents with a positive asthma history or siblings with respiratory problems, since these characteristics are associated with higher risk of asthma in the future. Proponents of sodium cromoglycate assume that it is effective in 'allergic asthma'; however, we have never found a definition of allergic asthma, nor studies in children that showed atopy or allergies as predictors of success of treatment with cromoglycate. An indication for a confining role of atopy in the effectivity of cromoglycate was concluded by Edwards, who found some evidence of greater efficacy when sputum eosinophilia was present.[11] However, in the review by Hoag and McFadden, atopy did not influence the overall outcome of sodium cromoglycate treatment.[12]

Dose prescribed

A three times daily dose was chosen in our protocol because this regimen was considered suitable in the daily program of families with young children. In the Netherlands a four times daily dose is recommended in children and adults,[13] but

in the UK sodium cromoglycate is recommended three times daily.[3] The reason for this difference in recommendations is not clear.

Spacer device and dose delivered

How much of the medication actually reached the lungs of the children is unknown, but this does not invalidate the conclusions about treatment as advised in guidelines and as it is commonly practised. It is well known that only a small proportion of the drug sprayed into a spacer device actually reaches the lungs and that the variation between spacer devices can be large, and relatively unfavourable for the Aerochamber®. Nevertheless, using a spacer device is the preferred way to administer inhalation medication to young children and effectivity of salbutamol, administered with an Aerochamber®, has been demonstrated.[14,15] The amount of salbutamol delivered from spacer devices was similar to the amount of sodium cromoglycate.[16] In addition to that, both Comis and Novembre and their colleagues have shown that 10 mg cromoglycate, given by Nebuhaler® and Volumatic®, respectively, is effective in the prevention of exercise-induced asthma in school-aged children.[17,18] Because the size of the spacer is probably less important in young children[19], it is unlikely that the use of an Aerochamber® contributes importantly to the negative outcome of our study.

Subjective outcome measure

As was the case in diagnosing asthma, symptoms were the main outcome measures for effectiveness. Validated symptom assessments in research of childhood asthma are lacking. The influence of symptom perception of the parents on recordings of symptom assessments is expected to be large. Tools to adjust for influences like this are unknown. Being aware of this limitation, an overall symptom measurement should include the frequency, duration and magnitude of symptoms.[20] Beside the proportion of symptom-free days, several other outcome measures from the parental symptom score lists as well as from the interview at the monthly home visits, were analysed in our study. It is debatable whether other, more objective, measures of morbidity would be superior to symptoms, since the latter are directly related to the burden of the disease.

Beside the fact that symptom-scoring systems for use in young children are not validated against objective parameters of disability, none has been validated for objective measures of airflow obstruction. Development of portable equipment, which enables airway function to be measured with a mouthpiece or a facemask while the child is breathing normally, might be a useful clinical tool. Such a procedure should be easy and applicable in the home situation. Standardisation of the technique is ongoing.[21]

Treatment period

In general it is recommended to use sodium cromoglycate for a period of six weeks before deciding whether it is effective or not. The follow-up period of our trial was five months and outcome measures were based on months 2-5 of the intervention period. There was no time-treatment interaction. In our systematic review of all published placebo-controlled trials in children with asthma (chapter seven), half of the trials (n=11) investigated preschool children; five trials showed benefit of cromoglycate, five showed equal results and one trial was partly positive, partly equal. Although duration of treatment periods was not a predictor of outcome in all trials, it was noteworthy that only one of the positive trials among preschool children had a treatment period of more than four weeks. In a review of (non-placebo controlled) studies investigating the effect of inhaled sodium cromoglycate on bronchial hyperresponsiveness in asthmatic children and adults, less reduction was shown in studies conducted for six weeks or less.[12]

Power

Enough children were included to prove our negative finding. In case the trial treatment had resulted in a 20% symptom reduction, we would have had a 98% chance to confirm this, given our sample size. Such a statistical power is rarely reached in clinical trials.
In conclusion, there seems to be little reason to doubt the negative result of our trial showing that children 1-4 years old will not benefit from prophylactic inhalation therapy with cromoglycate via the Aerochamber®.

We conclude from our trial and review on sodium cromoglycate that the place for this drug in the therapeutic arsenal of long-term prophylactics for asthmatic children has been overvalued. Through history, it seems that sodium cromoglycate has achieved an eminent place in anti-asthma prophylaxis in children, mainly because of research in open trials, crossover studies published before 1980 and in studies of the immediate effects on exercise induced asthma, but not based on evidence from more recent placebo-controlled trials. In our systematic review we did not include studies on the immediate effects of cromoglycate on exercise-induced asthma or studies on the effects of combined therapy like the corticosteroid sparing effects of cromoglycate, considering these regimens not to pertain to the use of sodium cromoglycate as advised by current guidelines for children of all ages.

Conducting a clinical trial in general practice

Failure of trials is mostly caused by disappointing practical and organisational aspects. The successful development of our trial can mainly be attributed to the

fact that the researchers were independent of the participating general practitioners and were in charge of most of the practical aspects of the trial organisation like enrolment and approaching the patients, data collection and follow-up. Computerisation of the medical records of patients in general practice offers an easy way to select patients for research. Since, in our case, children with asthma could be selected from data on specific treatment, enrolment from the computerised medical records of the general practitioners was possible. Research concerning prevalent diseases could enrol patients by searching medical records on diagnoses, specific medication or symptoms. In a trial that requires patients with incident illness, a preliminary selection like ours would not be possible and researchers would be dependent on general practitioners for enrolment of their patients. Nevertheless, even in trials on recurrent incident illnesses or complaints, the computer can help by indicating to the general practitioner that this might be an eligible patient for the trial. A subsequent screen could show telephone numbers of the research team, questions for initial data collection or informed consent and by 'on-line communication' the researchers could be contacted and take over further selection, inclusion and data collection.

Though time consuming, the direct patient contacts were another advantage of our trial setting. Home visits by the researchers instead of hospital visits by the patients (possibly parents with young children) have minimised the number of patients lost to follow-up. Collecting data from patients probably works best without interposition of caregivers. Computer technology can also be important in data collection. In 1998, 9% of the overall Dutch population possessed an Internet connection, this number has increased by 43% in the last year.[22] It is feasible that patients could e-mail their daily symptoms, questionnaires or measurement scores (from own computers or from handheld computers distributed by the researchers) to a main trial computer or enter them on a secured site. Even voice response units 'calling' patients at agreed times and collecting the data in files that are ready to be analysed, can be envisaged.

Because computerisation in Dutch general practices is much more developed than in hospitals, and information and communication technology continue to develop, we expect that research in general practice will become increasingly accessible and continue to expand.

Determinants of children who continued using inhaled prophylactic treatment

In chapter six, predictors for use of prophylactic inhalation treatment eight months after the trial were found in patient characteristics obtained by history taking and differences in morbidity during the trial. Realising that 'use' of inhaled

prophylactic therapy at follow-up can not be directly translated into 'need' for this treatment, most of the significant characteristics in our short-term follow-up correspond with predictors for future asthma in cohorts that are followed at larger intervals.[23-25] Several characteristics, that are easily obtained by history taking, may help physicians who care for young children with asthma: they can predict which children will 'need' prophylactic inhalation therapy for a longer period.

To close the final chapter of this thesis it can be concluded that

- prophylactic inhalation therapy in children under the age of four years is feasible but sometimes problematic. Alternatives with other routes of administration must be evaluated and giving anti-asthma medication based on symptoms would have the best compliance.
- effectivity of inhaled sodium cromoglycate could not be demonstrated in young children with moderate asthma; the value of cromoglycate seems to have been exaggerated in previous years and by previous guidelines.
- validation of asthma symptom scores in all age groups, but especially in children under the age of four, is required against disability and symptom perception as well as against objective lung function measures.
- general practice can be an excellent setting for prospective research, even for large randomised placebo-controlled trials, and use of computerised methods improves its applicability and feasibility.

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Summary

chapter one
Introduction

Respiratory diseases are a major cause of morbidity in children under the age of four years and reported prevalences of asthma and wheezing range from 10%-20%. In treating and investigating young children with asthma, physicians face many uncertainties regarding diagnosis, treatment and prognosis. Because objective measures of asthma are lacking, diagnosis and treatment are based on subjective measures like parental report of symptoms and physical examination. In children with asthma, symptoms, specific relief and/or prophylactic anti-asthma medication can be indicated, in preschool children preferably administered by inhalation with a metered dose inhaler and a spacer devices with face-mask. A drug recommended as first-line prophylactic is sodium cromoglycate, a well-known anti-inflammatory drug and without serious side effects. Treatment with inhaled steroids is increasingly used in moderate asthma, at the expense of cromoglycate. Inhaled steroids have shown effectivity, also in young children, but the long-term safety in young children remains to be established. Therefore, a potential role for cromoglycate in treating moderate asthma in young children still exists. Information on the effectivity of cromoglycate in young children with moderate asthma is lacking. Whether long-term prophylactic treatment is feasible in the home situation is unknown, patient and parent adherence and compliance have hardly been investigated.

The main aims of this thesis were to investigate the feasibility of prophylactic inhalation therapy with a spacer device and facemask in young children with moderate asthma in a general practice setting and to investigate the effectivity of sodium cromoglycate. Furthermore, characteristics of children who still used prophylactic inhalation treatment eight months after finishing the trial were studied. The execution of this type of clinical trial in general practice has also been critically evaluated.

chapter two
Identifying children with asthma in GP files

The aim of this first study was to find out whether children with asthma could be identified in the files of general practitioners (GP). Parents of all 464 children, 1-4 years of age, registered in five general practices received a mail questionnaire, asking about asthma symptoms experienced by the child, and past and present asthma medication. Using the answers, we classified the children as having no, mild, moderate or severe asthma according to current guidelines. The GPs' records were also checked, for recordings of asthma symptoms, specific asthma medication and asthma-related diagnoses. The presence of these items on GPs'

records was compared to asthma severity, as derived from the questionnaire answers. The questionnaire was filled in for 87% of the children.

All children with severe asthma were known to their GPs. The proportion of asthmatic children known to their GPs fell with decreasing severity of the disorder. Asthma symptoms and specific asthma medication were registered in medical records more often than asthma-related diagnoses. For all classes of severity combined, 75% of preschool children with asthma are known to their GPs. In the GPs' files, registered medication turned out to be the best way to identify children with asthma.

chapter three

Randomised controlled trial of sodium cromoglycate

The feasibility and effects of sodium cromoglycate inhalation therapy were studied in 218 children, aged 1-4 years with moderate asthma. They were recruited through 151 general practitioners between March 1995, and March 1996. They were randomly assigned sodium cromoglycate (10 mg three times daily) or placebo given by inhaler with spacer device and facemask (Aerochamber®) for 5 months. Rescue medication (ipratropium+fenoterol aerosol) was available during the baseline period of 1 month and during the intervention period. Parents completed a daily symptom-score list during six months. The primary outcome measure was the proportion of symptom-free days in months 2 to 5. Analysis was by both intention to treat and on treatment. A total of 167 (77%) children completed the trial; 131 (78%) of these used at least 80% of the recommended dose. Of the children who stopped prematurely, 23 had difficulties with inhaled treatment. The mean proportion of symptom-free days for both groups was greater for the treatment period than for the baseline period (95% CI for mean difference 5.1 to 17.5 cromoglycate, 11.9 to 23.3 placebo). However, there were no differences between the sodium cromoglycate and placebo group in the proportion of symptom-free days (mean 65.7 [SD 25.3] vs. 64.3 [24.5]%; 95% CI for difference -8.46 to 5.70) or in any other outcome measure. Our study in a general practice setting shows that inhalation therapy with a spacer device and facemask is feasible in a majority of children below the age of four years. However, long-term prophylactic therapy with inhaled sodium cromoglycate is not more effective than placebo in this age group.

chapter four

Conducting a clinical trial in general practice

The practical aspects of conducting the randomised clinical trial in primary care are described and the discrepancies between planning and reality are addressed. By taking over most time-consuming activities, such as recruitment, randomisation and follow-up we were able to avoid the pitfalls of research in general practice: unsuccessful recruitment and withdrawal of GPs and/or patients. We enrolled patients from computerised medical records of the GPs based on data on prevalent illness. Direct contact with all eligible patients and their caregivers enabled us to provide uniform documentation on the difference between eligible and enrolled patients.

chapter five

Feasibility of prophylactic inhalation therapy

The purpose of this study was to further investigate the feasibility of and the compliance with long-term prophylactic inhalation therapy in children aged 1-4 years with moderate asthma. Outcome measures for feasibility were willingness to participate in the trial, loss of participants during the trial, and compliance. Compliance was assessed by weighing the canisters and by means of parental daily reports. Of all invited parents (n=449) one third refused to participate in the trial due to expected feasibility problems. A total of 232 children started the baseline period and 167 children completed the trial; of this latter group 78% used 80% or more of the prescribed medication. No difference in drug use was found between the cromoglycate and the placebo group. Compared to the weight loss of the canisters the parents underreported medication use. There was a relationship between the number of symptoms and the compliance on the same day. Presence of eczema was a predictor for better compliance. During the trial 51 children dropped out prematurely, 30 of these because of feasibility problems. Predictors for these withdrawals were younger age of the child and lower education level of the mother. Long-term inhalation therapy with spacer device and facemask is feasible in children aged 1-4 years and compliance can be relatively high in a selected and well-supported group. Physicians should be aware that a considerable proportion of parents of preschool children with moderate asthma are reluctant to start, or will discontinue, long-term prophylactic inhalation therapy.

chapter six

Follow-up of the children

This study investigates whether characteristics of children still using inhaled prophylactic therapy (sodium cromoglycate or steroids) at follow-up, can be found. A total of 208 children classified as having moderate asthma were contacted 14 months after they started the previously described clinical trial, eight months after finishing the trial. Patient characteristics from history taking at the start of the trial and morbidity characteristics from parental reports during the trial were analysed and predictors for long-term use of inhaled prophylaxis were found: perception of exercise as a precipitant for respiratory symptoms, sibling(s) with asthmatic symptoms, a maternal history of asthma, less attendance at day-care, more frequent and longer episodes with respiratory symptoms and more GP consultations for respiratory reasons. Characteristics of preschool children still using inhaled asthma prophylaxis after one year correspond with characteristics for persisting asthma as found in long-term follow-up studies.

chapter seven

Systematic review of sodium cromoglycate

We systematically reviewed all published randomised placebo-controlled trials on prophylactic treatment with sodium cromoglycate in children with asthma. Randomised placebo-controlled trials were identified by means of Medline, Embase, the Cochrane Controlled Trial Register, and by selecting references from relevant articles. The database of the pharmaceutical company producing sodium cromoglycate was also consulted. The methodological quality of the studies was assessed by the scoring method of Chalmers. The 95% confidence intervals of differences in symptom score between placebo and sodium cromoglycate treatment were computed. The 95% estimates were pooled and tested for homogeneity; in order to explain heterogeneity we evaluated the influence of study characteristics on the outcome and made a funnel plot. A total of 22 randomised placebo-controlled trials were identified in which methodological scores ranged from 24%-79% of the maximum attainable total. The major shortcomings of the studies were in "selection and inclusion", "compliance" and "analysis". Statistical pooling of 95% confidence intervals was possible for mean difference in symptom scores in 20 studies, and for mean relative improvement in 19 studies. The null-hypothesis of homogeneity was rejected. Year of publication of the study was a determinant of a positive study result, which means that older studies concluded more often in favour of cromoglycate. For heterogeneity, the overall tolerance interval included zero, thus it can not be concluded that sodium cromoglycate is superior to placebo. These findings support the decision of guidelines

committees to withdraw the recommendation of sodium cromoglycate as the first choice for inhaled prophylactic asthma treatment in children.

chapter eight
General discussion

We conclude that inhalation therapy with a spacer device and facemask is feasible, and compliance can be relatively high, even in a long-term trial with a three times daily regimen and a drug that proved to be not more effective than placebo. On the other hand, the parents in the study were selected and well motivated. A considerable proportion of young children need effective anti-asthma drugs that can be administered in a different way. The randomised placebo-controlled trial was successfully conducted in general practice, as the most appropriate setting for investigating inhalation therapy in young children with moderate asthma, due to a study design that minimised the workload for participating general practitioners. Increasing computerisation, information and communication technology makes medical research in the home situation more accessible and feasible. Neither the trial results nor the systematic review of all published placebo-controlled trials on inhaled sodium cromoglycate treatment in children with asthma, showed an overall beneficial effect of the drug. Therefore, this thesis provides additional evidence for national and international guidelines to withdraw the recommendation of sodium cromoglycate as the first choice in first-line inhaled prophylactic treatment. Long-term prophylactic inhalation therapy with cromoglycate shows no clinically relevant benefit in young children with asthma.

Samenvatting

hoofdstuk een

Inleiding

Aandoeningen van de luchtwegen zijn het meest voorkomende gezondheidsprobleem bij jonge kinderen; astma is de meest voorkomende chronische aandoening. Onder de leeftijd van vier jaar wordt, gebaseerd op het symptoom, vaak gesproken van 'wheeze'. Gerapporteerde prevalenties van astma en wheeze variëren van 10% tot 20%.

Bij het behandelen en het bestuderen van jonge kinderen met astma ondervinden artsen een aantal onzekerheden ten aanzien van de diagnose, behandeling en prognose. Omdat objectieve uitkomstmaten van astma vrijwel ontbreken, worden de diagnose en de behandeling gebaseerd op meer subjectieve maten, zoals de door de ouders waargenomen symptomen en het lichamelijk onderzoek. Voor kinderen met astmasymptomen kan specifieke symptomatische en/of profylactische anti-astmamedicatie geïndiceerd zijn; voor jonge kinderen bij voorkeur toegediend met een dosis aerosol (spuitbusje) met behulp van een voorzetkamer met gezichtsmasker.

Cromoglycaat is een ontstekingsremmend medicament zonder ernstige bijwerkingen, geadviseerd als een middel van eerste keuze ter voorkoming van aanvallen (zgn profylacticum). In plaats van cromoglycaat wordt behandeling met inhalatiesteroïden ter profylaxe van astma meer en meer geadviseerd en toegepast. Inhalatiesteroïden hebben bewezen effectiviteit, ook bij jonge kinderen, maar de veiligheid op langere termijn is nog niet geheel duidelijk. Daarom zou er nog steeds een rol voor cromoglycaat bij de behandeling van jonge kinderen met astma kunnen bestaan. De effectiviteit van cromoglycaat bij kinderen van 0-4 jaar met matig ernstig astma is onbekend. Of langetermijn profylactische behandeling haalbaar is in de thuissituatie en hoe de therapietrouw is, is vrijwel niet onderzocht.

Onderzoek naar de haalbaarheid van profylactische inhalatie-therapie via een voorzetkamer met gezichtsmasker bij jonge kinderen met matig ernstig astma in een eerstelijns setting alsmede het onderzoeken van de effectiviteit van cromoglycaat zijn de doelstellingen van dit proefschrift. Verder worden kenmerken van kinderen die acht maanden na het onderzoek nog profylactische inhalatietherapie gebruiken onderzocht. Het uitvoeren van een vergelijkend geneesmiddelenonderzoek (een zogenaamde trial) in huisartsenpraktijken wordt geëvalueerd.

hoofdstuk twee

Het identificeren van kinderen met astma uit huisartsenregistraties

Het doel van deze eerste studie was uit te vinden of kinderen met astma konden worden geïdentificeerd in de registraties van huisartsen. De ouders van alle 1- tot 4-jarige kinderen (n=464) uit vijf huisartsenpraktijken ontvingen per post een vragenlijst over eventuele astmasymptomen van hun kind, en eventuele astma-medicatie nu of in het verleden. Met de antwoorden op deze vragen werden de kinderen, in overeenstemming met astmarichtlijnen, geclassificeerd als hebbende geen, mild, matig ernstig of ernstig astma. Daarnaast werden de dossiers van de huisartsen bekeken op geregistreerde astmasymptomen, specifieke astma-medicatie en aan astma gerelateerde diagnosen. Het aanwezig zijn van deze items in de huisartsendossiers werd vergeleken met ernst van het astma, zoals gebaseerd op de antwoorden op de vragenlijsten.

De vragenlijst werd ingevuld door de ouders van 87% van de kinderen. Alle kinderen met ernstig astma bleken als zodanig bekend bij hun huisarts. De proportie kinderen, bekend bij hun huisarts, nam af met de ernst van het astma. Astmasymptomen en specifieke astmamedicatie werden meer in de medische dossiers geregistreerd dan astmagerelateerde diagnosen. De huisarts was bekend met 75% van alle kinderen met astma gebaseerd op de vragenlijst (alle klassen van astma te samen). Het zoeken op medicatie, geregistreerd door de huisarts in het patiëntendossier, bleek de beste manier om kinderen met astma te identificeren.

hoofdstuk drie

Een gerandomiseerde, dubbelblinde, placebo-gecontroleerde trial met cromoglycaat

We bestudeerden de haalbaarheid en effectiviteit van inhalatietherapie met cromoglycaat in 218 1- tot 4-jarige kinderen met matig ernstig astma. Zij waren geselecteerd uit de praktijken van 151 huisartsen tussen maart 1995 en maart 1996. Het toeval bepaalde of zij cromoglycaat (3maal daags 10mg), hetzij placebo kregen, beide in dosis aerosolen en toegediend via een voorzetkamer met gezichtsmasker (Aerochamber®). Voor situaties van benauwdheid van hun kind kregen de ouders noodmedicatie (ipratropium+fenoterol aerosol) ter beschikking tijdens de baseline periode van een maand en tijdens de interventieperiode van vijf maanden. De ouders hielden gedurende deze zes maanden dagelijks een symptoomscorelijst bij. De primaire uitkomstmaat was de proportie symptoomvrije dagen in maand 2-5 van de interventieperiode. 167

(77%) kinderen gebruikten gedurende de hele interventieperiode de onderzoeksmedicatie; 131 (78%) van hen gebruikte meer dan 80% van de voorgeschreven dosis. Van de kinderen die voortijdig stopten, hadden 23 problemen met de inhalatietherapie. De gemiddelde proportie symptoomvrije dagen van zowel de cromoglycaat- als de placebogroep was hoger tijdens de behandelperiode dan in de baseline periode. Er waren echter geen verschillen tussen de beide groepen in proportie symptoomvrije dagen, noch in enige andere uitkomstmaat. Onze studie in de huisartsensetting laat zien dat inhalatietherapie met een voorzetkamer haalbaar is bij de meerderheid van de kinderen onder de leeftijd van vier jaar. Echter, langetermijn profylactische behandeling met geïnhaleerd cromoglycaat is niet effectiever dan behandeling met placebo bij deze kinderen.

hoofdstuk vier

Het uitvoeren van een trial in de huisartsenpraktijk

In dit hoofdstuk worden de praktische aspecten van het uitvoeren van een trial in de eerste lijn beschreven en worden discrepanties tussen planning en realiteit geëvalueerd. Omdat we tijdrovende, met het onderzoek samenhangende activiteiten zoals selectie van de kinderen, randomisatie en follow-up, van de huisarts overnamen, omzeilden we de valkuilen van onderzoek in de huisartsenpraktijk, namelijk tegenvallende patiëntenwerving en het terugtrekken van huisartsen en patiënten tijdens het onderzoek. We selecteerden de kinderen door in de gecomputeriseerde patiëntendossiers te zoeken op gegevens over prevalente gezondheidsproblemen, namelijk astma en wheeze. Het directe contact van de onderzoekers met de ouders van alle geselecteerde kinderen maakt het mogelijk een goed beeld te krijgen van het traject van selectie naar deelname aan de trial en succesvolle voltooiing van de studie.

hoofdstuk vijf

Haalbaarheid van inhalatietherapie

Het doel van deze studie was de haalbaarheid en de therapietrouw met langdurige profylactische inhalatietherapie bij 1- tot 4-jarige kinderen met matig ernstig astma verder te bestuderen. Uitkomstmaten voor haalbaarheid waren mate van bereidheid om deel te nemen aan de trial, uitval van deelnemers gedurende de trial en de therapietrouw. Deze laatste werd bepaald door het gewicht van de medicijnbusjes (canisters) én door de notitie van de ouders op de dagelijkse scorelijst. Van alle ouders die uitgenodigd waren mee te doen aan de trial (n=449) weigerden er 72, omdat zij op voorhand problemen met het inhale-

ren verwachtten. 232 kinderen startten de baseline periode van de trial en 167 van hen bleven gedurende de hele trialperiode de onderzoeksmedicatie gebruiken. 78% van hen gebruikte meer dan 80% van de voorgeschreven dosis.

We vonden geen verschil tussen het medicatiegebruik in de cromoglycaatgroep en de placebogroep. Vergeleken met het gewichtsverlies van de canisters was er sprake van onderrapportage van het medicatiegebruik door de ouders. Het aantal gerapporteerde symptomen op een dag toonde een positief verband met het (profylactisch) medicatiegebruik. Bij kinderen met eczeem was sprake van een betere therapietrouw. Dertig van de 51 kinderen die voortijdig met de onderzoeksmedicatie stopten, deden dat vanwege haalbaarheidsproblemen. Deze kinderen waren jonger en hun moeder had gemiddeld een lager opleidingsniveau.

Samengevat blijkt langetermijn inhalatietherapie met een voorzetkamer met gezichtsmasker haalbaar voor 1- tot 4-jarige kinderen en de therapietrouw is relatief hoog in deze geselecteerde en goed begeleide groep. Een aanzienlijk deel van de ouders van jonge kinderen met matig ernstig astma zal echter opzien tegen starten of stoppen met de inhalatietherapie.

hoofdstuk zes

Follow-up

Het doel van deze studie was na te gaan of de kinderen die 8 maanden na het stoppen van de trial nog profylactische inhalatietherapie gebruiken, zich onderscheiden van de kinderen die geen profylactische astmamedicatie meer inhaleren. In totaal werden de ouders van 208 kinderen met matig ernstig astma ondervraagd, 14 maanden nadat zij de trial startten en 8 maanden na het beëindigen ervan. Patiëntengegevens, verkregen bij de anamnese aan het begin van de trial en gegevens uit de dagelijkse symptoomscorelijsten en de maandelijkse interviews gedurende de trial, werden geanalyseerd. De volgende kenmerken bleken samen te hangen met aanhoudend gebruik van profylactische inhalatiemedicatie: inspanning als uitlokker van luchtwegsymptomen, broers/zussen met astma, een moeder met astma, minder dagopvang, frequentere en langere episoden met luchtwegsymptomen en meer huisartsbezoeken in verband met luchtwegklachten. Deze kenmerken komen overeen met voorspellers van aanhoudende astma zoals beschreven in langetermijn follow-up studies.

hoofdstuk zeven

Systematische review van cromoglycaat

Doel van deze studie was een overzicht op te stellen van alle goed uitgevoerde studies met cromoglycaat als (langetermijn) profylactische behandeling van kinderen met astma. Alle gepubliceerde gerandomiseerde placebogecontroleerde trials werden opgespoord en bestudeerd. De studies werden geïdentificeerd door middel van Medline, Embase, het Cochrane Controlled Trial Register en referenties van reeds gevonden artikelen. Ook werd de database van de farmaceutische industrie die cromoglycaat vervaardigt geconsulteerd. De methodologische kwaliteit van de studies werd bepaald aan de hand van de scorelijst van Chalmers en de verschillen in symptoomscores tussen placebo- en cromoglycaatbehandeling werden berekend. De uitkomsten van de verschillende studies werden samengenomen en getest op homogeniteit; we evalueerden de invloed van studiekenmerken op de uitkomst om de heterogeniteit te verklaren en maakten een zogenaamde funnel plot. De methodologische scores van de 22 gevonden trials varieerden van 24% tot 79% van de maximaal te verkrijgen score. De grootste tekortkomingen werden gevonden voor de onderdelen 'selectie en inclusie', 'compliantie' en 'analyse'. Samennemen van de resultaten was mogelijk voor 20 studies. De nulhypothese van homogeniteit werd verworpen. Het jaar van publicatie bleek een determinant van een positief studieresultaat; oudere studies gaven een groter effect van cromoglycaat te zien. In verband met de heterogeniteit berekenden wij een tolerantie-interval. Deze bleek de nulwaarde te omvatten, zodat we niet kunnen concluderen dat cromoglycaat effectiever is dan placebo.

hoofdstuk acht

Discussie

We concluderen dat inhalatietherapie met een voorzetkamer met gezichtsmasker haalbaar is voor 1- tot 4-jarige kinderen met astma en dat de therapietrouw relatief hoog kan zijn, zelfs in een langdurige trial met een driemaal daagse dosering en een medicament dat niet effectiever bleek te zijn dan placebobehandeling. Opgemerkt moet worden dat de ouders en kinderen in de studie geselecteerd en goed gemotiveerd waren. Een aanzienlijk deel van de jonge kinderen zou beter uitkomen met effectieve anti-astmamedicamenten die niet per inhalatie toegediend hoeven worden. De gerandomiseerde trial werd succesvol uitgevoerd in de eerste lijn - de juiste omgeving om inhalatie-therapie in jonge kinderen met matig ernstig astma te onderzoeken - door een studiedesign dat de werkbelasting voor de participerende huisartsen beperkt hield. Toenemende computerisatie, informatie- en communicatietechnologie maken onderzoek in de thuissituatie toegankelijker. De trialresultaten noch de bevin-

dingen van de systematische review van alle gepubliceerde placebogecontroleerde trials over inhalatie met cromoglycaat voor kinderen met astma, lieten een positief effect van het middel zien. Daarmee ondersteunen de bevindingen uit dit proefschrift de terugtrekking van het advies met betrekking tot cromoglycaat als therapie van eerste keus voor de profylaxe van astmasymptomen bij kinderen.

Dankwoord

Het belangrijkste onderdeel van mijn promotie-onderzoek is de trial. Ik wil dan ook allereerst alle kinderen en hun ouders heel hartelijk danken voor hun, vaak enthousiaste, deelname. Het is uiteindelijk niet niets om een half jaar lang driemaal daags met je peuter te inhaleren, symptoomscorelijsten in te vullen en regelmatig onderzoekers thuis te ontvangen.
Honderdeenenvijftig huisartsen stelden hun praktijk voor ons 'open' om de kinderen met astma te rekruteren en te vervolgen. Marjon van Huuksloot en Nel de Jonge hebben honderden huisbezoeken gedaan en op de meest gekke plaatsen moeders opgespoord om niet aan 'lost to follow-up' toe te geven. Het was een plezier om met hen samen te werken.
Naast mijn promotor Prof.dr Johan de Jongste, bestond de vaste begeleidingsgroep van de trial uit Hans van der Wouden, Lisette van Suijlekom-Smit en Ben Ponsioen. Johan de Jongste wil ik heel hartelijk danken voor het inhoudelijk sturen van het project; eerst de trial en later het proefschrift. Toen Johan hoogleraar werd, zongen zijn collegae van de de afdeling kinderlongziekten een lied over de commentaren van zijn hand, meestal geschreven met dé vulpen. Ik had toen geen idee wat dit betekende, nu wel. Opvallend was niet de kwantiteit van het commentaar maar de opbouwende kwaliteit en helderheid ervan. Ook de samenvattende opmerkingen als "OK", "leuk voor een huisartsenblad", "te wordy", "niet goed" of "prima stuk" waren volledig duidelijk.
Hans van der Wouden was als coördinator kinderlijn de begeleider van de dagelijkse lopende zaken. Zowel de samenwerking als de zaken liepen prima, vooral door zijn humor, bereikbaarheid, zijn altijd open deur en snelheid van werken. Samen met Lisette, de kinderarts van de originele ideeën en praktische zaken, gingen we naar een congres in Tours waaraan ik goede herinneringen heb. Met Ben Ponsioen deelde ik de kamer op het instituut en hij was altijd druk, geïnteresseerd en enthousiast. Later deelde Roos Bernsen ook die kamer, schreef mee aan vrijwel alle hoofdstukken en tekent voor de statistiek. Ongelooflijk hoe zij wildwest-ideeën in een model kan gieten, analyseren, antwoorden geeft en dat allemaal ook nog duidelijk kan uitleggen.
Sita Biema-Zeinstra, mijn buurvrouw aan de overkant en promovendus in dezelfde fase, wil ik bedanken voor de bewaking van ons beider promotieproces. Als zij niet een half jaar voor de einddatum tegen mij had gezegd; 'Je moet alles wat je klaar hebt eens in een map doen, dan lijkt het al wat...', dan was het boekje nu nog niet af. Bovenal wil ik Roos en Sita bedanken voor de vriendschap en gezelligheid; die gaan hopelijk door.
Siep Thomas werd in 1997 hoogleraar huisartsgeneeskunde in Rotterdam en in een later stadium promotor van dit project. Hij promootte vooral duidelijkheid, opbouw en de rode draad.
Alle mede-onderzoekers van het huisartsinstituut wil ik bedanken voor de hulp, interesse en vooral voor de goede werksfeer. Dat geldt trouwens ook voor alle

andere medewerkers van het instituut, zeker die van het secretariaat. Speciaal Pien Schubert en later Trudy van de Pol hebben veel voor de studie gedaan. Met veel genoegen kijk ik op de afgelopen vier jaar terug en ik kan me niet heugen met tegenzin te hebben gewerkt.
De grondlegger van het trialprotocol is Hans Uijen; dat gebeurde vóór mijn tijd aan het instituut, maar enkele jaren later werd het meeschrijven aan de review een deel van zijn huisartsopleiding. Hoewel het schrijven van reviews onderzoekers erg somber kan maken, was dit bij ons niet het geval. We hebben erg veel gelachen en ik kan me geen onderwerp bedenken dat we niet hebben gereviewd.
Het Astmafonds financierde de hoofdstudie, Fisons (later Rhône-Poulenc Rorer) leverde de onderzoeksmedicatie en Boeringer Ingelheim leverden de rescuemedicatie en de voorzetkamers. Zelfs ná de resultaten en conclusies bleef de verstandhouding met Fisons plezierig. Het Instituut voor Medische Statistiek wil ik noemen omdat zij belangeloos gegevens beschikbaar stelden om inzicht te krijgen in voorschrijfcijfers van astma-medicatie.
Laraine Visser-Isles wil ik hartelijk bedanken voor de Engelse correcties, Anna Bosselaar voor de layout van het proefschrift en Iris de Jong voor het omslagontwerp.
Van het thuisfront wil ik allereerst Henk Willem bedanken voor zijn liefdevolle support en de continue bereidheid om kruizen te zetten in zijn agenda. En eigenlijk óók allereerst wil ik Joke Jansen-Kerklaan bedanken voor deze coproductie. Al jaren is zij oppas voor de kinderen en steunpilaar van ons gezin. Het is een voorrecht naar het werk te gaan in de wetenschap dat het thuis gezellig is en dat alles 'als vanzelf' doordraait. Mijn moeder en schoonouders en Truus Jongman spelen daarbij een enorm belangrijke rol en hen dank ik voor alle liefde, gezelligheid, hulp, opvang en leuke uitjes.
Beate Walhof, hartsvriendin vanaf klas 1g, en Jan Kees van der Kamp, hartszwager van de late telefoongesprekken, waren meteen bereid paranimf te zijn (Beate liet zelfs 'Mexico' lopen). Ik vind het heel bijzonder met hen 'te staan'.
Andere vrienden en familie toonden altijd interesse en speciaal mijn broers dank ik voor hun gezonde onbegrip en goede, niet-wetenschappelijke adviezen.
Goof, Wietske en Thijs dank ik voor de tekeningen op het omslag en voor het feit dat zij steeds weer duidelijk maken dat waar het wérkelijk om gaat meestal niet in boekjes staat.

About the author

Marjolein Tasche was born on August 15, 1959 in Hengelo, Overijssel. After graduating high school in 1977 at the Twickel College in Hengelo, she started physical therapy studies in Groningen and graduated in 1981. That same year she began Medical studies, also in Groningen, and had a part-time job as a physiotherapist in Delfzijl. From the fourth year of medical study she transferred to Erasmus University Rotterdam and graduated cum laude in 1988. After one year dermato-pathology at the Leids Cytologic and Pathologic laboratory in Leiden and one year occupational medicine at a newly founded service for health institutes in Rotterdam, she started vocational training for general practitioner in 1990. This was completed in 1992, including two periods of maternity leave. She worked as a deputy in general practices in Schiedam and Vlaardingen from 1993 to 1997, and in 1994 she began as a GP researcher at the department of General Practice in Rotterdam, performing and evaluating the project that resulted in this thesis.

She is married to Henk Willem van der Kamp and they live in The Hague with their three children: Goof, Wietske and Thijs.