Continuous and on demand use of bronchodilators in patients with non-steroid dependent asthma and chronic bronchitis: four-year follow-up randomized controlled study

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SUMMARY

Background. *A previous two-year study of continuous and on demand bronchodilator therapy in patients with moderate asthma and chronic bronchitis showed a deterioration in lung function in those on continuous therapy.*

Aim. *A two-year follow-up study was undertaken of patients who had been shown in the previous study to have non-steroid dependent (mild) asthma and chronic bronchitis, in order to investigate the effect of continuous and on-demand treatment with bronchodilator therapy.*

Method. *Patients for the study were drawn from 29 general practices in the catchment area of the University of Nijmegen, the Netherlands. A total of 83 patients (27 with asthma and 56 with chronic bronchitis) were selected from a group of 160 patients who had completed the previous two-year bronchodilator trial. During these first two years the selected subjects had been shown to be non-steroid dependent (no rapid decline in lung function and a low number of exacerbations of their condition per year), and they were followed up for another two years of treatment with bronchodilator therapy. At the start of the four-year study, patients were randomly assigned to one of two parallel treatment groups: continuous treatment (dry powder inhalations of either salbutamol 1600 µg or ipratropium bromide 160 µg daily) or treatment on demand (only during exacerbations or periods of dyspnoea). Outcome parameters were the annual decline in lung function, changes in peak flow rate, bronchial hyper-responsiveness, exacerbation rate, respiratory symptoms and reported health.*

Results. *After correction for possibly confounding variables and for regression to the mean, the decline in lung function was 49 ml year^{-1} in patients taking bronchodilators continuously and 51 ml year^{-1} in patients using bronchodilators on demand, irrespective of the drug used. Continuously treated patients, whether suffering from asthma or chronic bronchitis, did not differ from patients treated on demand with respect to mean morning peak flow rate, diurnal (and week to week) variation of the peak flow rate, bronchial hyper-responsiveness, exacerbation rate and reported health. There was no difference between the long-term effects of salbutamol and ipratropium.*

Conclusion. *Continuous use of bronchodilators over four years in patients with non-steroid dependent asthma or chronic bronchitis does not increase the decline in lung function which had been observed previously in patients with moderate asthma or chronic bronchitis during two years of continuous treatment with bronchodilators.*

Keywords: asthma; bronchitis; bronchodilators; drug administration; drug dosage; lung function.

Introduction

EPIDEMIOLOGICAL studies of patients with moderate or severe asthma or chronic bronchitis have pointed to an association between the prescription of beta$_2$-adrenergic drugs and death from asthma.[1,2] Although epidemiological studies cannot provide evidence that bronchodilators themselves increase asthma mortality, these studies have caused considerable concern about the possible deleterious effects of long-term continuous use of bronchodilators. This concern increased when two prospective randomized trials were published which showed an increase in bronchial hyper-responsiveness[3] and in decline in lung function[4] with continuous use of bronchodilators. These and earlier observations led to the recommendation in several international guidelines only to use bronchodilators on demand.[5,6] It is not clear whether the continuous use of bronchodilators over a period of several years might also have deleterious effects in patients with mild asthma or chronic bronchitis.

General practice patients with mild asthma or chronic bronchitis might be non-steroid dependent and most of these patients in the Netherlands are treated with bronchodilators only[7] as is probably the case in many other countries. It could be that the adverse effects of the continuous use of bronchodilators are not, or are less clearly, present in patients with non-steroid dependent asthma or chronic bronchitis. Thus far, adverse effects have mainly been reported with beta$_2$-adrenergic drugs. It is important to assess whether these effects are common to all bronchodilators.

The first aim of this study was to investigate the effect of continuous and on demand treatment with bronchodilators over four years in patients with non-steroid dependent asthma or chronic bronchitis. The second aim was to compare the long-term effects of the anticholinergic drug ipratropium bromide with those of the beta$_2$-adrenergic drug salbutamol. The sample of patients was drawn from the population of patients who had already been followed for two years.[4]

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Method

Patients

The study began in 1987. Patients aged 30 years and over were drawn from 29 practices in the catchment area of the University of Nijmegen, the Netherlands. A description of the original patient selection is given elsewhere.[4] Of 223 participating patients, 160 completed the first two years of bronchodilator treatment.[4] It was considered unethical to continue bronchodilator treatment in patients who had been shown to need additional anti-inflammatory medication because of a clear progression of their disease. Therefore 56 patients (27 using bronchodilators on demand and 29 using them continuously) with a rapid decline in forced expiratory volume in one second (FEV_1) ($\geqslant$80 ml $year^{-1}$) and an exacerbation rate of more than one episode per year were withdrawn from this study and received an inhaled corticosteroid.[8] The remaining 104 patients were asked to continue in the study for another two years with only bronchodilator treatment. These patients were considered non-steroid dependent. Of these patients 21 refused to participate and 83 continued. All of the 21 patients who refused did so because of personal reasons unrelated to their disease. Their clinical status was not different from the 83 patients who continued the study.

The criteria for the diagnosis of asthma or chronic bronchitis were based on those of the American Thoracic Society.[9] Asthma was defined as the combination of: bronchial hyper-responsiveness to histamine (provoking concentration of histamine that produces a 20% decrease in FEV_1 (PC_{20}) $\leqslant$8 mg histamine ml^{-1}); reversible airways obstruction (FEV_1 improved by more than 15% of the pre-bronchodilator value 60 minutes after the administration of both salbutamol 400 µg and ipratropium bromide 80 µg); dyspnoea; allergy (at least one positive test out of seven of the most common radioallergosorbent tests) and/or wheezing. Chronic bronchitis was defined as the combination of: chronic cough or chronic sputum production for at least three months during at least two consecutive years; and continuous bronchus obstruction (FEV_1 $\leqslant$85% of the predicted value[10]).

Although separate features of asthma and chronic bronchitis were not mutually exclusive (for example, some asthma patients had chronic cough and some chronic bronchitis patients had a PC_{20} $\leqslant$8 mg ml^{-1}, the combination of features was such that no patient with asthma also had chronic bronchitis and vice versa.

Study design and treatment protocol

The study was approved by the medical ethics committee of the University of Nijmegen. All patients gave informed consent. At the start of the four-year intervention study, and after an eight-week washout period patients were randomly allocated to one of two parallel treatment regimens: continuous bronchodilator therapy (four times daily) or treatment on demand (only during periods of complaints).[4] During the first two years the patients used dry powder inhalations of salbutamol 400 µg during one year and of ipratropium bromide 40 µg during the other year. The sequence of the drugs was determined by random allocation. During the third and fourth years, the 83 patients continued the medication they had been taking in the second year.

Patients had to record all the medication they used in a diary. Once every three months throughout the study period, the inhalation technique as well as compliance with the prescribed medication were checked by the general practitioner or practice assistant. Any deviations from the protocol were discussed immediately with the patients. A separate, single-blind, prospective study was carried out assessing bronchodilator therapy compliance among patients who used the drug continuously. Compliance was measured by research investigators who counted capsules at the end of a randomly chosen four-month period.[11] Assessment of compliance continued independently of this substudy; patients were unaware that their medication was being counted after this period.

Lung function, bronchial responsiveness and airways reversibility

All measurements were carried out by two qualified laboratory assistants during exacerbation-free periods. No bronchodilator was inhaled for at least eight hours before the pulmonary function tests. The FEV_1, bronchial responsiveness to histamine (PC_{20} histamine values) and the reversibility of airways obstruction were assessed at six-month intervals by means of the Microspiro HI-298® (Chest Corporation).[12] The FEV_1 and airways reversibility were also assessed after one and 13 months of study.[4] The best of three forced expiratory manoeuvres, with the highest sum of the forced vital capacity and FEV_1, was used for data analysis. Bronchial responsiveness to histamine was measured according to the method described by Cockcroft and colleagues.[13]

Peak expiratory flow rate assessments and exacerbations

Once a week, peak expiratory flow rate measurements were performed with the Assess® peak flow meter (Healthscan Products)[14] at home in the morning and evening, on the same day and at the same time. The highest value out of three measurements was taken for analysis. The diurnal peak expiratory flow rate index (absolute difference between evening value and morning value divided by the highest value) and the week-to-week variation in the peak expiratory flow rate (the standard deviation expressed as percentage of the mean morning peak flow in three months) were calculated.

Exacerbations were defined according to Fletcher with the small modifications of Boman and colleagues,[15] and comprised (muco)purulent sputum, cough and at least one of the following symptoms: general malaise, symptoms of common cold, fever, dyspnoea, increased sputum production, increased sputum thickness, foul-tasting sputum or increased difficulty in expectorating. In case of an exacerbation, a 10-day course with oral prednisolone was given. Patients received 25 mg for two days, 20 mg for two days, 15 mg for two days, and so on.

Symptoms, health and smoking habits

Respiratory symptoms were assessed by means of a Medical Research Council questionnaire at the beginning, after 24 months and at the end of the study, and quantified on a scale of 0–8.[7] Additionally, all patients made weekly recordings of the presence and severity of symptoms (cough, phlegm, dyspnoea) on a scale of 0–4.

Health (energy, pain, emotions, sleep, social limitations and mobility problems) was assessed by means of the Nottingham health profile at the start of the study, after 24 months and at the end of the study.[16] At the start of the study, smoking history was assessed in pack years (by multiplying number of years smoking cigarettes and reported number of cigarettes smoked per day, divided by 20). During the study, the average number of cigarettes smoked per day was also recorded in the diary every week.

Power calculations

On the basis of the earlier study[4] it was assumed that a clinically relevant difference in decline in FEV_1 (the primary effect parameter) between the two parallel treatment groups was 40 ml $year^{-1}$ or more. With a residual standard deviation of 60 ml $year^{-1}$ the coefficient of variation is 40/60. With an alpha of 0.05 (one

sided) and a beta of 0.20 (power of (1 – 0.2) = 0.8), the required number of patients per group was 30. With an estimated drop-out rate of 20%, the required initial number of patients in both groups was 36.

Analysis

Values of outcome variables between the two treatment groups were tested by multivariate analysis of variance for normally distributed variables and the Wilcoxon test for not normally distributed variables. All FEV_1 and PC_{20} values were adjusted for smoking behaviour before and during the study, for sex, age, height, allergy, initial FEV_1 (% predicted) and initial PC_{20}. Prior to analysis, the PC_{20} values were ^{2}log transformed. The annual changes in FEV_1 and PC_{20} were calculated by linear regression of individual FEV_1 and $^2\log PC_{20}$ values in the course of time. To determine the group values, the individual regression coefficients were averaged. The weekly measured peak expiratory flow rate was averaged for three-month periods. Patients with asthma and chronic bronchitis were analysed together and separately.

Of the 83 patients who completed the study, six patients did not use the planned study medication or used additional medication. Therefore, both explanatory analysis (only those patients included who used only the study medication) and intention to treat analysis (all patients included) were performed. Unless these two analyses had different outcomes, only the results of the intention to treat analysis are given.

In the present study design, patients were not randomly selected from the original study population: only patients with a less severe form of the disease were selected. By chance these patients might have deteriorated during the third and fourth years when compared with the two first years of treatment. This phenomenon is called regression to the mean. The influence of regression to the mean was calculated for both treatment groups in separate analyses. The effect of regression to the mean was estimated by the equations of Davis.[17]

The effects of ipratropium and salbutamol on all outcome parameters were assessed by comparing the effects during years two to four, as the medication had been crossed after the first year. This was only done if no interaction effect between the treatment regimen and the drug could be detected.

Results

Baseline characteristics

Of the 83 patients who completed the four-year study, 77 completed it with the planned study medication. Of the other six patients, five needed additional medication in the fourth year, (three received an inhaled steroid and two were given sodium cromoglycate) and one refused to continue taking salbutamol continuously in the fourth year. These six patients were not excluded from the study. At the start of the study there was no statistically significant difference between these six patients and the other 77 patients.

Of the 83 patients, 27 had asthma and 56 had chronic bronchitis. There were significantly more smokers among patients with chronic bronchitis than among patients with asthma, and asthma patients were significantly more likely to have an allergy (Table 1). Of the patients who completed the four-year study 36 were taking bronchodilators continuously and 47 were taking bronchodilators on demand. In the second, third and fourth years of the study, 48 patients were on ipratropium, of whom 21 were taking it continuously, and 35 were on salbutamol of whom 15 were taking it continuously. The four treatment groups were comparable in every respect at the start of the four-year intervention study (Table 1).

Bronchodilator use, and smoking behaviour during study

Patients treated on demand used a median of 0.1 (range 0.1–2.0) dry powder inhalations of salbutamol per day and 0.1 (range 0.1–1.3) inhalations of ipratropium per day, which was not significantly different. The single-blind study of compliance among patients on continuous bronchodilator medication showed that mean individual compliance rates were 98% (standard deviation 29%) of the prescribed medication.

The median number of cigarettes smoked during the study by patients using bronchodilator therapy on demand was 0 per day (range 0–28) and by patients using bronchodilators continuously, four per day (range 0–21) ($P<0.05$).

Lung function

Grouping patients with asthma and chronic bronchitis together, the annual decline in FEV_1 over the four years was 70 ml year^{-1}

Table 1. Baseline characteristics of patients who completed the study, according to diagnosis and treatment in the second, third and fourth years of the study.

	Patients with		Patients receiving			
			Salbutamol		Ipratropium	
Variable	Asthma (*n* = 27)	Chronic bronchitis (*n* = 56)	On demand (*n* = 20)	Continuously (*n* = 15)	On demand (*n* = 27)	Continuously (*n* = 21)
Mean (SD) age (years)	51 (12)	53 (14)	49 (13)	54 (17)	50 (14)	57 (9)
No. of men	15	34	8	10	17	14
No. with asthma/ chronic bronchitis	27/0	0/56	8/12	6/9	6/21	7/14
Median no. (range) of of pack years	6 (0–75)	12 (0–81)	8 (0–73)	15 (0–75)	7 (0–81)	18 (0–52)
No. of smokers	18	48*	15	12	20	19
Mean (SD) respiratory symptom score	4.7 (1.9)	4.6 (1.7)	4.9 (1.7)	4.8 (2.0)	4.6 (1.9)	4.3 (1.6)
No. with allergy	11	10*	8	4	8	1
Mean (SD) FEV_1 (l)	2.4 (0.9)	2.6 (0.9)	2.6 (0.8)	2.3 (0.9)	2.7 (0.9)	2.3 (0.8)
Median (range) reversibility (% FEV_1 predicted)	*15 (0–54)*	*6 (0–40)***	*9 (0–25)*	*11 (1–47)*	*8 (0–40)*	*7 (0–54)*
PC_{20} (mg histamine ml^{-1})	2.9	15.2***	8.8	7.1	13.8	7.9

n = number of patients in group. SD = standard deviation. Difference between patients with asthma and chronic bronchitis: *$P<0.05$, **$P<0.01$, ***$P<0.001$.

in patients using bronchodilators on demand and 60 ml year^{-1} in patients using bronchodilators continuously. This difference was not significant (10 ml, 95% confidence interval (CI) –21 to 41 ml year^{-1}). After correction for possibly confounding variables the decline was 66 ml year^{-1} in patients using treatment on demand and 65 ml year^{-1} in patients using treatment continuously. The estimated regression to the mean effect was approximately the same in both groups: 29 ml year^{-1} in patients using treatment on demand and 32 ml year^{-1} in patients using treatment continuously. After correction for this regression effect the annual decline over the four years was 51 ml year^{-1} among patients taking bronchodilators on demand and 49 ml year^{-1} among patients using bronchodilators continuously.

The mean change in FEV_1 and standard error over the four years for patients with asthma are shown in Figure 1, and for those with chronic bronchitis in Figure 2 (while the standard error is plus and minus the mean, in order to keep the figures clear, the standard error has been marked as plus the mean for patients on treatment on demand, and minus the mean for patients on continuous treatment). Patients who used bronchodilators on demand did not differ significantly from those treated continuously (corrected mean values for asthma: 21 ml year^{-1} versus 58 ml year^{-1} respectively, and for chronic bronchitis: 85 ml year^{-1} versus 60 ml year^{-1} respectively).

The mean decline in FEV_1 among patients on salbutamol was not significantly different from the mean decline among among those using ipratropium (difference 2 ml year^{-1}, 95% CI –71 to 75 ml year^{-1}).

Peak expiratory flow rate

During the study the mean morning peak expiratory flow rate of asthma patients using bronchodilators continuously did not differ significantly compared with patients using treatment on demand (15 ml year^{-1} CI difference, 95% –10 to 40 ml year^{-1}), nor was there a difference in diurnal index between the two groups, the mean diurnal index in patients using bronchodilators on demand being 11.6% and in those using bronchodilators continuously 10.4% (difference 1.2%, 95% CI –2.9% to 5.3%). The week to week variation in peak expiratory flow rate in asthma patients using treatment on demand was not significantly different from that of patients using treatment continuously (12.4% versus 10.6% respectively, difference 1.8%, 95% CI –1.1% to 4.7%).

Among patients with chronic bronchitis no difference was observed in the mean morning peak flow according to treatment method (difference 2 ml year^{-1}, 95% CI –12 to 16 ml year^{-1}). The mean diurnal index among patients with chronic bronchitis using bronchodilators continuously was 8.5% and among patients using treatment on demand 6.1% (difference 2.4%, 95% CI –0.1% to 4.9%). The week to week variation in peak expiratory flow rate was 8.6% in both groups of patients.

Among patients using salbutamol, mean morning peak expiratory flow rate was 405 l min^{-1}, which was not significantly different from the mean morning rate of 428 l min^{-1} among those using ipratropium (difference 23 l min^{-1}, 95% CI –30 to 76 l min^{-1}). The same applied to the diurnal index of the peak expiratory flow rate (9.3% versus 7.2%, respectively) and to week to week variation (8.5% versus 8.3%, respectively).

Bronchial hyper-responsiveness

The course of PC_{20} for patients with asthma and chronic bronchitis is shown in Figure 3. Among patients with asthma, there was a slight increase in bronchial hyper-responsiveness in patients treated on demand: the mean change in PC_{20} over the four years was –0.64 doubling dose of histamine per year. In patients using bronchodilators continuously it was 0.01 doubling dose per year

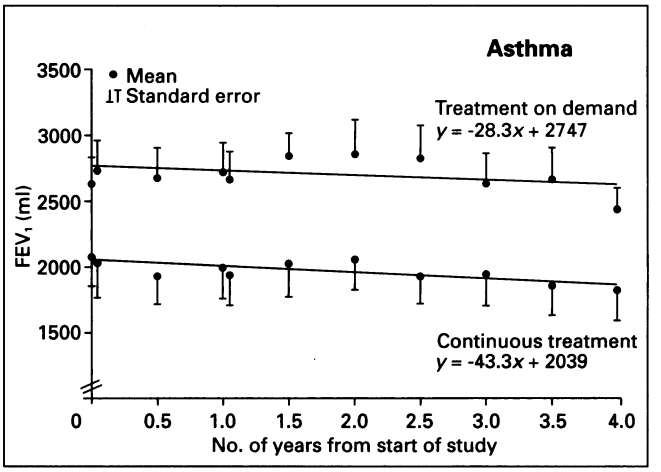

Figure 1. *Course of FEV_1 (mean and standard error) over four years in patients with asthma, of whom 13 were on continuous and 14 were using on demand treatment.*

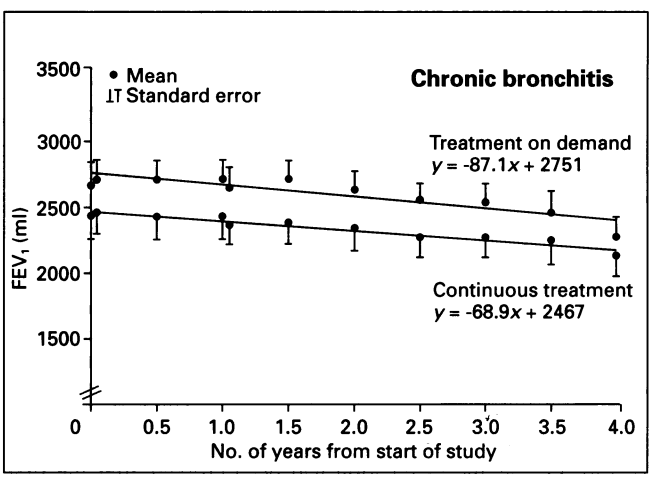

Figure 2. *Course of FEV_1 (mean and standard error) over four years in patients with chronic bronchitis of whom 23 were on continuous and 33 were using on demand treatment.*

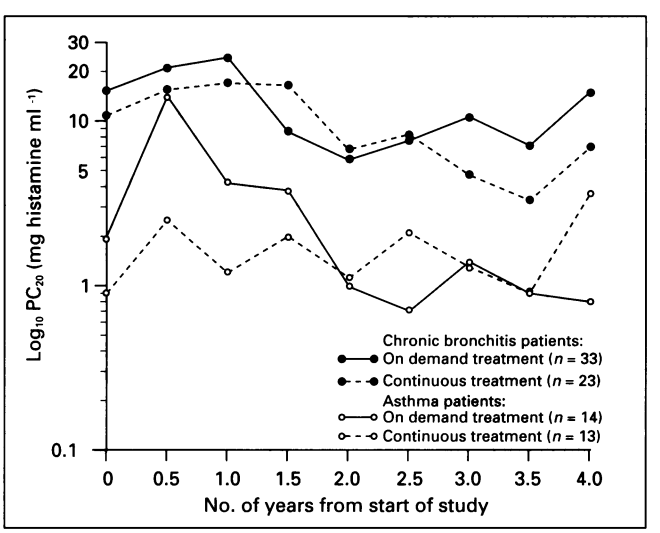

Figure 3. *Bronchial hyper-responsiveness (course of PC_{20}) over four years in patients with asthma and chronic bronchitis (n = number of patients).*

(difference 0.65, 95% CI –0.09 to 1.39 doubling dose per year). In patients with chronic bronchitis these changes were comparable (–0.36 versus –0.44 doubling dose per year, respectively).

Among patients using salbutamol, the mean change in PC_{20} for asthma was –0.29 doubling dose per year, which was not significantly different from the mean change of –0.51 doubling dose per year among patients using ipratropium (difference 0.22, 95% CI –0.77 to 1.21 doubling dose per year). Among patients with chronic bronchitis there was an increase in PC_{20} when salbutamol was used and a decrease when ipratropium was used (0.44 versus –0.94 doubling dose per year, respectively). This difference was significant (1.38 doubling dose per year, 95% CI 0.27 to 2.44 doubling dose per year).

Exacerbations

During the study the number of exacerbations in patients who used bronchodilators on demand decreased from 0.7 in the first year to 0.5 in the fourth year. The number of exacerbations in those taking bronchodilators continuously showed an opposite trend: an increase from 0.5 to 0.7 from the first to the fourth year. However, the difference was small and non-significant. There was no difference between patients with asthma and chronic bronchitis in this respect.

The mean number of exacerbations in patients using salbutamol was not significantly different from the number in those using ipratropium (0.6 versus 0.5 exacerbations per year, respectively).

Recorded symptoms and health

The severity of weekly recorded symptoms decreased in patients using bronchodilators on demand when compared with those using bronchodilators continuously (difference 0.4 points per year on the symptom score, 95% CI 0 to 0.8 points per year). When respiratory symptoms were measured on the Medical Research Council questionnaire this observation was confirmed: a decrease of 0.3 points per year in patients using bronchodilators on demand which differed significantly from the increase of 0.1 point per year in patients using bronchodilators continuously (difference 0.4, 95% CI 0.1 to 0.7 points per year).

The weekly symptom score showed the same change among those using salbutamol as among those using ipratropium (a decrease of 0.1 point per year).

Health as measured on the Nottingham health profile was not influenced by treatment regimen or by drug.

Discussion

The main results of this study indicate that continuous use of bronchodilators over four years in patients with non-steroid dependent asthma or chronic bronchitis does not seem to increase decline in lung function. This is contrary to the observations in a previous study in which patients with steroid-dependency were included.[4]

It is important to assess what may have caused the difference between the findings in the present study of patients with non-steroid dependent asthma and chronic bronchitis and those in the earlier studies in which increased hyper-responsiveness[3] and increased decline in lung function[4] were found among those using bronchodilators continuously. The most likely explanation is in the selection of patients for the present study: only those patients who had been shown to be non-steroid dependent during the first two years of study were selected. The hypothesis was that in these patients the possibly harmful effects of continuous use of bronchodilators would not be (or would be less clearly) present.

The present study does not seem to point to a direct link between the continuous use of bronchodilators and an increase in asthma morbidity or mortality, the so-called asthma paradox.[18] Although at present there is evidence of a possible correlation between the use of bronchodilators and asthma-related death,[1,2] it is not probable that the relationship is causal in this way. It is more probable that overdependence on the $beta_2$-adrenergic drugs delays the use of necessary anti-inflammatory agents which then might be a cause of death from asthma.[19]

The results of the study should be interpreted with caution. The findings do not justify the conclusion that all patients with mild asthma or chronic bronchitis should be treated with only bronchodilators, without anti-inflammatory treatment. Five of the 83 selected patients (6%) who had been shown to be non-steroid dependent during the first two years needed additional anti-inflammatory medication in the fourth year. Moreover, it is not known what would have happened if all the patients in the present study had received additional anti-inflammatory treatment. As far as is known there is only one other long-term study in non-steroid dependent asthma.[20] That study clearly showed that bronchial hyper-responsiveness improved considerably during the 12-month use of an inhaled steroid in 15 of 16 asthmatic patients. On the other hand, the results of that study do not seem to justify the early introduction of inhaled steroids in all non-steroid dependent asthma patients. The 16 patients studied were selected when they attended a clinic because of pulmonary problems. Moreover, all of them used bronchodilators more than once daily. In the present study, 14 of the 83 patients (17%) had once attended a clinic for pulmonary problems and only 24 patients (29%) had used bronchodilators continuously before the start of the study.[4,7] The remaining patients had used bronchodilators on demand in the year preceding this four-year study.[4]

It is estimated that in the Netherlands[7] and in the United Kingdom[21] at least 80% of all patients with asthma or chronic bronchitis are treated in primary care. This is particularly so for patients with mild forms of asthma. On the basis of the results of the present study it seems probable that there are patients with mild forms of airway obstruction who do not (yet) need anti-inflammatory drugs. Symptomatic use of bronchodilators might be sufficient for these patients. The inflammatory processes underlying the progression of the disease are probably not at a stage where anti-inflammatory treatment is necessary. This is in accordance with recently developed guidelines which advise anti-inflammatory treatment when bronchodilators are needed on a regular basis (more than once daily).[5] In a random sample of patients with asthma or chronic bronchitis in primary care it was observed that only 42% used bronchodilators continuously.[7] This figure shows that there may be a considerable number of patients who are in an early phase of the disease and who do not yet need anti-inflammatory drugs. As it is still not clear whether chronic use of inhaled steroids will have important side effects in the long run, caution is necessary in prescribing drugs on a long-term basis.

It is difficult to know how to distinguish between patients who do and do not need anti-inflammatory medication. This problem is even more complicated because of the low correlation between the progression of the disease and the perception of symptoms[22] and experienced health.[16] It seems that most patients learn to live with their asthma or chronic bronchitis.[23] Therefore, it is important to instruct patients to consult their physician when they need to use their bronchodilators daily.[5] The general practitioner should be advised to prescribe anti-inflammatory drugs to these patients and, if necessary, to refer these patients to a specialist.

In order to detect patients with a rapid progression of asthma and chronic bronchitis in primary care, regular testing of pulmonary function in general practices is advised. In this study the 56 patients who were found to be steroid-dependent after two years were detected on the basis of regular lung function testing.[24] These 56 patients were part of the original group of 223

patients (25%) who at the start of the study were considered to be non-steroid dependent by their general practitioner.[4] Additional treatment with steroids clearly slowed down the deterioration caused by asthma and chronic bronchitis in these patients.[8]

The definition of asthma and chronic bronchitis was based on the standards of the American Thoracic Society.[9] The accuracy of this definition was confirmed by the results of this study: as expected, the yearly decline in lung function was at least twice as high in patients with chronic bronchitis as in those with asthma, despite the more impaired clinical condition of the asthma patients, at the start of the study (shown by their lung function, airways reversibility and bronchial hyper-responsiveness values). Moreover, it was observed that asthma patients had a higher diurnal variation of the peak flow, they smoked less before and during the study and they responded much better to inhaled corticosteroids.[8] Smoking behaviour, diurnal variation of the peak flow and steroid responsiveness were not used in the present study's definition criteria, but are all important characteristics for distinguishing between asthma and chronic bronchitis.

One of the problems in such a study is that the selection procedure could have biased the results. Patients with a rapid decline in lung function (≥ 80 ml year^{-1}) and an exacerbation rate of more than one episode per year were excluded from participation in this study.[8] Because of this one-sided selection procedure the decline in lung function of the patients participating in this study may have increased because of statistical reasons unrelated to the disease (regression to the mean effect). The data for the decline in lung function were corrected for this effect. The most important question is whether the regression effect in patients treated on demand was different from that of patients treated continuously. As these effects were comparable it can be concluded that the selection procedure did not bias the main results of the study.

The second aim of this study had been to compare the long-term effects of salbutamol and ipratropium bromide. There was no difference between the drugs in all the investigated parameters, with one exception: bronchial hyper-responsiveness decreased with the use of salbutamol and increased with the use of ipratropium in patients with chronic bronchitis. It is difficult to give an explanation for this finding, but it may be explained by the inhibition of mediator release from neutrophils, which has been found in *in vitro* experiments.[25] As patients with chronic bronchitis who smoke are known to have elevated numbers of neutrophils in bronchoalveolar lavage fluids and biopsies,[26] this might explain the favourable effect of salbutamol on hyper-responsiveness in chronic bronchitis. However, a more likely explanation is that it is just a coincidental finding, as multiple comparisons were made in this study.

In conclusion, the continuous use of bronchodilators over four years in patients with non-steroid dependent asthma or chronic bronchitis does not seem to increase the decline in lung function as had been observed in patients with moderate asthma or chronic bronchitis. There was no difference found between the long-term effects of salbutamol and ipratropium bromide.

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