ORIGINAL ARTICLE

Treatment compliance, passive smoking, and asthma control: a three year cohort study

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Aims: To study the role of treatment compliance and parents' smoking on asthma control in children with recently diagnosed mild or moderate persistent asthma who were prescribed inhaled anti-inflammatory treatment.

Methods: Prospective cohort study of 167 children aged 6–12 years (64% boys). Patients were examined at inclusion and followed up for three years with a visit every four months. Peak expiratory flow (PEF) was measured twice a day during the week before each visit. Two control criteria were monitored: (1) symptom control = having diurnal or nocturnal exacerbations less than once a week and no symptoms between exacerbations, at all visits; and (2) PEF control = daily PEF variability <20% on each of the seven days before each visit.

Results: Symptom control was achieved by 25.1% of children and PEF control by 53.3%. Symptom control was positively related to having understood the way in which the medication worked and taking the prescribed doses (odds ratios (OR) = 3.38 and 4.82 respectively). It was inversely related to smoking within the home (OR = 0.34). PEF control was positively related to taking the prescribed doses (OR = 3.58). It was less frequently achieved if the mother smoked within the home (OR = 0.34).

Conclusions: Results suggest that, to maximise the benefits of available asthma medication and to improve health outcomes, further efforts should be made to convince the parents of asthmatic children not to smoke in the house, and to improve compliance by increasing the patients' understanding of the disease and its treatment.

Asthma is the most common chronic disease in childhood; it may affect up to 35% of the population in developed countries.[1] Asthma is an inflammatory disease of the airways involving respiratory symptoms, such as wheezing and coughing, and reversible airflow limitation. Its severity differs widely between patients, but most people with asthma have a mild form of the disease.[2 3]

International guidelines have been established for the management of asthma,[4] based on a classification of asthma severity (before treatment) into four grades: intermittent, mild persistent, moderate persistent, and severe persistent. Inhaled anti-inflammatory medication is recommended for all patients with persistent asthma.[4 5] The goal of management is to achieve control: symptoms, whether diurnal or nocturnal, should be absent or minimal with infrequent exacerbations, and pulmonary function should be normal.[4] To achieve this, patients with persistent asthma should take anti-inflammatory medication as prescribed, even if they have no symptoms.

It should be possible to achieve control, whatever the initial severity stage,[4 6] except in a few difficult/therapy resistant cases.[7] However, in clinical practice, appropriate prescriptions do not result in asthma control in all patients; the reasons for this are not known. Identification of the personal or environmental characteristics of patients that are associated with the achievement of asthma control would be of great value for all doctors involved in asthma management. There is some epidemiological evidence of the role of compliance to treatment for adult patients: two studies showed that suboptimal use of inhaled steroids and overconfidence in β_2 agonists were associated with increased risk of acute asthma episodes and of hospital admission.[8 9] In contrast, such studies for children are scarce. Milgrom *et al* recruited 24 children attending a specialist outpatient clinic and followed them for 13 weeks: they found that underuse of inhaled corticosteroids was related to more frequent need for oral steroid courses.[10] The associations between passive smoking and asthma morbidity in children have been more extensively investigated, but with inconsistent results.[11 12] Moreover, few of these studies have adjusted for potential confounding variables.[12]

The objective of this cohort survey was to study the role of treatment compliance and of parents' smoking on asthma control in children with recently diagnosed mild or moderate persistent asthma, prescribed inhaled anti-inflammatory treatment. Other family, personal, and environmental factors were taken into account.

PATIENTS AND METHODS

Chest specialists throughout France were asked by regional medical associations to participate in this three year prospective cohort survey and to include the first two children aged 6–12 years, examined between 1 March and 30 November 1995, that met the inclusion criteria. Inclusion criteria were: (1) documented asthma diagnosed during the inclusion visit or no more than 12 months previously (that is, recurrent episodes of wheezing or coughing with either a 15% increase in forced expiratory volume in one second (FEV_1) after bronchodilator use, or a 20% decrease in FEV_1 after bronchoconstrictor challenge); (2) $FEV_1 \geq 60\%$ of the predicted value at the inclusion visit; and (3) informed consent obtained from the parents for participation in a three year study.

Criteria for exclusion were: (1) having a chronic respiratory disease other than asthma; (2) treatment with high doses of inhaled corticosteroids (≥ 750 µg/day) for one month or longer at the time of inclusion; and (3) having unstable asthma (that is, asthma exacerbations during the past three months involving emergency care or systemic corticosteroids for 15 days or

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; OR, odds ratio; PEF, peak expiratory flow

more). The exclusion criteria were aimed at excluding patients with severe or difficult asthma, which might have biased the results.[13]

At inclusion, each patient was given a new Mini-Wright peak flow meter (Clement Clarke, Harlow, UK), was instructed in its use, and told to record the highest peak expiratory flow (PEF) of three measurements for each timepoint.

During the three year follow up period, patients were examined every four months. They measured PEF on getting up (before inhaling β_2 agonists) and in the evening, for a week before each visit, and recorded the measurements in a diary.

Data were collected by means of detailed standardised questionnaires completed by physicians. The initial questionnaire included questions concerning the patient's socio-demographic background, personal history of allergy (seasonal or perennial rhinitis, atopic dermatitis), and family history of asthma, lifestyle, and environmental factors (exposure to tobacco smoke, moulds, or animals; type of bedding and flooring; cooking appliances). The physicians also reported the results of atopy tests (skin prick tests or specific IgE) and lung function tests, carried out according to usual clinic practice, and the medication prescribed for asthma. Most questions were derived from the ECRHS questionnaire.[14] The follow up questionnaires completed at each visit included questions concerning changes in lifestyle and environment, possible severely negative life events, and the medication prescribed. Questions focusing on environmental tobacco smoke assessed whether at least one person smoked in the home, and if yes, if it was the father, the mother, brothers or sisters, or another person. Standardised questions focusing on treatment compliance assessed: (1) whether the patient understood how each drug worked; (2) whether the patient ever forgot to take the drugs; (3) whether the patient took the prescribed doses without either decreasing or increasing them; and (4) the doctor's opinion concerning whether the patient's technique for taking inhaled medication was adequate.

In both the initial and follow up questionnaires, asthma symptoms were assessed using questions developed from the international guidelines,[4] concerning the frequency of asthma attacks (diurnal and nocturnal) and the occurrence of wheezing or coughing between the attacks. The same questions were asked at each visit.

The protocol was approved by local ethics authorities and by the National Committee for Data Processing and Freedom.

Two hundred and fifty one chest specialists participated in the study; they included a total of 334 children, as many specialists did not have two patients that met the inclusion criteria for the protocol (especially for recent diagnosis).

Statistical analysis

Because international guidelines suggest that optimal treatment is achieved several months after diagnosis,[4] we took the third follow up visit (one year after inclusion) as the starting point for assessing control. The 201 children that were on anti-inflammatory medication at that time were considered to have persistent asthma and were eligible for this study. Eighty three of these patients attended all six visits scheduled for the second and third years of follow up, 46 attended five, 21 attended four, 17 attended three, and 34 attended less than three. We analysed only the 167 (83%) children that had attended at least three visits (mean 5.2). These children did not differ from the other 34 eligible children in age, sex, symptom severity, sensitisation to allergens, allergic rhinitis, dermatitis, or family history of asthma.

We used two independent control criteria:

- "Symptom control" was satisfactory if the child had diurnal and nocturnal asthma less than once a week and had no symptoms between attacks, at all visits in the second and third years.
- "PEF control" was satisfactory if daily PEF variability was <20% each of the seven days before each visit.[4] Daily PEF variability was calculated as (maximum PEF – minimum PEF)/mean PEF, %).

For personal characteristics we analysed the data collected at inclusion. Lifestyle and environmental factors were considered to be present if they were reported at inclusion or at any time during follow up (there were very few changes after inclusion). Each of the four variables indicating compliance was considered to be positive if compliance was achieved at all visits in the second and third years.

We used the SAS-PC statistical package (SAS Institute Inc, Cary, NC, USA). In a preliminary univariate analysis, contingency tables were analysed using the χ^2 test, and two tailed Fisher's exact test if numbers were small, to select the factors to be considered for the final multivariate analysis. In multiple logistic regression analyses with symptom control or PEF control as dependent variables, we included the factors that were associated in the univariate tests with p values <0.20. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the association between outcome and the explanatory factors.

RESULTS

Table 1 presents the characteristics of the 167 children studied and the factors considered in the analysis. Mean age was 9.5 years (SD 2.0). Most patients (93%) were atopic and sensitisation to more than one allergen was very frequent: 17.1% of the

Table 1 Characteristics of the study population (n=167)

	%
Age >10 years	35.3
Boys	64.1
Father's occupation	
Manager	8.9
Clerk	53.7
Manual labourer	20.3
Other	17.1
Atopic	93.1
Sensitised to mites	79.3
Sensitised to cats or dogs	33.3
Sensitised to pollen	54.1
Sensitised to moulds	20.8
Perennial asthma (with or without seasonal exacerbations)	59.9
Perennial allergic rhinitis (with or without seasonal AR)	51.2
Seasonal allergic rhinitis (with or without perennial AR)	19.3
Atopic dermatitis	34.3
Family history of asthma	
Father	19.6
Mother	24.7
Siblings	17.7
Gas used for cooking	89.0
Moulds on walls within the home	16.3
Dog within the home	34.1
Cat within the home	17.1
Wall to wall carpets	58.4
Woollen mattress	13.1
Allergy proof mattress cover	6.0
Passive smoking	
At least one smoker within the home	35.8
Mother smoking within the home	21.2
Compliance	
Understands how medication works	67.1
Does not forget to take the drugs	34.1
Takes the prescribed doses	52.1
Adequate technique for use of inhalers	48.5

AR, allergic rhinitis.

Table 2 Factors associated with symptom control or PEF control in univariate analysis

	Symptom control (%)			PEF control (%)		
	No (n=125)	Yes (n=42)	p value	No (n=78)	Yes (n=89)	p value
Age >10 years	35.2	35.7	0.95	28.2	41.6	0.07
Boys	68.8	50.0	0.03	61.5	66.3	0.52
Sensitised to mites	81.2	73.8	0.31	84.0	75.0	0.16
Sensitised to pollens	54.7	52.4	0.79	61.3	47.6	0.08
Perennial asthma	60.0	59.5	0.95	70.5	50.6	0.01
Perennial allergic rhinitis	54.8	40.5	0.11	48.7	53.4	0.54
Seasonal allergic rhinitis	21.7	11.9	0.16	17.9	20.4	0.68
Atopic dermatitis	35.5	30.9	0.59	46.1	23.9	0.003
Family history of asthma: father	22.5	10.5	0.11	22.4	17.1	0.40
Gas cooker	86.9	95.1	0.15	90.9	87.2	0.45
Moulds within the home	16.9	14.3	0.69	25.6	7.9	0.002
Wall to wall carpets	62.1	47.6	0.10	57.7	59.1	0.85
Passive smoking						
At least one smoker within the home	40.6	21.4	0.03	39.7	32.2	0.31
Mother smoking within the home	23.6	14.3	0.20	30.8	12.6	0.004
Compliance						
Understands how medication works	60.8	85.7	0.003	61.5	71.9	0.16
Takes the prescribed doses	45.6	71.4	0.004	37.2	65.2	0.001
Adequate technique for inhaler use	44.0	61.9	0.05	47.4	49.4	0.80

Table 3 Odds ratios and 95% confidence intervals for the association between symptom control and possible explanatory factors (multiple logistic regression)

	OR	95% CI	p value
Girls versus boys	1.86	0.76 to 4.53	0.17
Perennial allergic rhinitis	0.51	0.21 to 1.28	0.16
Seasonal allergic rhinitis	0.35	0.10 to 1.22	0.10
Father's history of asthma	0.33	0.10 to 1.18	0.09
Gas cooker	1.69	0.29 to 9.78	0.56
Wall to wall carpets	0.71	0.29 to 1.75	0.45
Passive smoking			
Smoker within the home	0.34	0.13 to 0.91	0.03
Compliance			
Understands how medication works	3.38	1.18 to 9.64	0.03
Takes the prescribed doses	4.82	1.87 to 12.40	0.002
Adequate technique for use of inhalers	1.59	0.67 to 3.81	0.29

atopic patients were sensitised to two allergens, and 75.3% to three or more. Asthma was diagnosed at the inclusion visit for 14 children (8.4%). Mean time from diagnosis to inclusion was 5.2 months (SD 4.0). The anti-inflammatory medication prescribed at the starting point for assessing control was corticosteroids >500 µg for 26.9% of children, corticosteroids ≤500 µg for 25.8%, and nedocromil or cromoglycate for 47.3%. Thirteen per cent of patients also had prescriptions for long acting β_2 agonists.

Symptom control was achieved by 25.1% of children and PEF control by 53.3%. There was a significant positive association between the two outcomes: 30 patients were positive for both, 59 for PEF control only, 12 for symptom control only, and 66 patients achieved neither ($p = 0.006$).

Table 2 shows the factors that were associated with either symptom control or PEF control with p values <0.20, in univariate analyses. Symptom control was positively associated with three variables expressing treatment compliance and inversely with the presence of at least a smoker in the home and with male sex. PEF control was positively associated with taking the prescribed doses and inversely with mother's smoking within the home, as well as with perennial asthma, atopic dermatitis, and moulds within the home. Seven children experienced a negative life event (parental separation for three, and death of a relative for four): no association was found between such events and asthma control.

In multiple logistic regression analysis, symptom control (table 3) was positively associated with having understood the way in which the medication worked and taking the prescribed doses (OR = 3.38, $p = 0.03$; and OR = 4.82, $p = 0.002$, respectively). It was inversely related to smoking within the home (OR = 0.34, $p = 0.03$). PEF control (table 4) was positively related to taking the prescribed doses (OR = 3.58, $p = 0.001$). It was less frequently achieved if the mother smoked (OR = 0.34, $p = 0.03$), but also if there were moulds within the home (OR = 0.33, $p = 0.05$).

Multiple logistic regression analyses restricted to the subgroup of 83 children that attended all six follow up visits confirmed the results reported above.

Finally, we compared the 32 children who achieved both symptom and PEF control with the 66 who achieved neither: the OR for understanding the way in which the medication worked was 5.31 (95% CI: 1.17 to 24.13), and the OR for taking the prescribed doses was 16.82 (95% CI: 4.11 to 68.94).

Table 4 Odds ratios and 95% confidence intervals for the association between PEF control and possible explanatory factors (multiple logistic regression)

	OR	95% CI	p value
Age >10 years	2.03	0.93 to 4.44	0.08
Sensitisation to mites	0.62	0.24 to 1.62	0.33
Sensitisation to pollens	0.48	0.23 to 1.03	0.06
Perennial asthma	0.69	0.31 to 1.53	0.36
Atopic dermatitis	0.51	0.23 to 1.15	0.11
Moulds within the home	0.33	0.11 to 0.97	0.05
Passive smoking			
Mother smoking within the home	0.34	0.14 to 0.89	0.03
Compliance			
Understands how medication works	1.49	0.68 to 3.29	0.32
Takes the prescribed doses	3.58	1.68 to 7.67	0.001

DISCUSSION

This three year study of a cohort of children recently diagnosed with mild or moderate persistent asthma and treated with inhaled anti-inflammatory drugs by chest specialists, showed that the control of asthma symptoms and of daily PEF variability was positively associated with treatment compliance (having understood the way in which each drug worked and taking the prescribed doses). Control was less frequently achieved in children exposed to tobacco smoke. Interestingly, it should be possible to manipulate the factors found to be associated with asthma control, to increase the efficacy of treatment.

The strength of this epidemiological study is to have followed up a large number of children with routinely treated persistent asthma, in the years following diagnosis. Moreover, the children were not recruited in a particular clinic or hospital, but were treated by a large number of doctors throughout France, which makes the results more generalisable. However, some limitations might be related to the recruitment of doctors or patients. The chest specialists that collected the data were asked by regional medical associations to participate in the study. This may introduce selection bias, which could have been avoided by selecting doctors randomly from a sampling frame of chest specialists. However, the level of participation in studies of this type is generally low. For example, for a study of the misuse of pressurised metered dose inhalers, we randomly selected a sample of general practitioners and chest specialists from the French medical profession directory. The participation rate among specialists was less than 40%.[15] Doctors interested in participating in epidemiological studies may treat their patients differently and may explain how the drugs work in more detail, but this is unlikely to bias associations between prognostic factors and disease outcome. The selection of patients by doctors would have been more problematic, but is very unlikely to have occurred as many doctors did not even reach the required number of eligible patients, because for most of their patients asthma had been diagnosed more than 12 months before the inclusion period. Although 334 patients were recruited according to the protocol, for this analysis of the role of treatment compliance we considered as eligible only the 201 children that were prescribed anti-inflammatory medication. Patients' participation was very good, since 167 (83%) of them attended at least three visits out of six in the second and third year of follow up (mean 5.2). The absence of association between asthma control and the category of anti-inflammatory medication prescribed suggests that the treatment was adequate despite 47.3% of the children being prescribed cromolyn instead of corticosteroids. The use of cromolyn as a first line therapy, particularly in those with milder disease, is encouraged by the results of a recently published study of a large cohort of children.[16]

The proportion of children that achieved asthma control was low for both outcomes. This can be explained by the definitions of control used in the analysis, which are conservative and would probably be considered as too stringent by many chest physicians in current practice. However, any definition would be arbitrary. We defined asthma control in terms of the clinical features described for intermittent asthma (step 1) in the international guidelines, given that in controlled asthma, symptoms should be absent or minimal and pulmonary function should be normal.[4 17] For lung function, we used daily PEF variability rather than PEF values. A marked increase in diurnal variability is a feature of poorly controlled asthma, whereas a decrease in PEF values is associated with asthma exacerbation.[18] The two types of control that we studied were positively associated but did not actually coincide, and twice as many children achieved PEF control as achieved symptom control. Previous studies have shown that changes in PEF variability during maintenance treatment with anti-inflammatory drugs are correlated to various extents with other indices of disease activity.[19–21]

A major finding of this study is the demonstration of an association between treatment compliance and asthma control. Although expected,[10 13] such an association has never before been documented in children outside clinical trials. Compliance with drugs is difficult to measure in epidemiological studies, especially if the questions are asked by the doctor who prescribed the treatment: the patients' desire to "please" their clinicians may result in an overestimate of self reported compliance with the prescribed treatment.[22] Various methods can be used to assess compliance with asthma therapies.[23 24] Self report of compliance is not a reliable measure of "objective" compliance as measured by actual canister or puff counts. However, the methods considered to be the most reliable could not be used in this observational study setting. Moreover, even with "objective" methods it is difficult to distinguish between actual use of the drug and drug "dumping" (the disposal of medication before a scheduled appointment).[22] Compliance level depends on the population studied, but also on the definitions used: it is therefore difficult to compare the results of different studies.[10 25] The compliance rates observed in this study seem reasonable, taking into account that participation in a clinical study may increase the patients' motivation and compliance.[25 26] Even if the definitions of compliance used in this study were debatable, they would have biased the results only if those with poorer control had reported poorer compliance, which is unlikely. Anyway, only such an observational study design is feasible to assess the effect of real world medication compliance on asthma control. Our data do not enable us to quantify the percentage of medication taken as prescribed, by

"compliers". However, for "compliers", self reported compliance was very good because it was considered to be positive only if it was achieved at all visits in the second and third years.

Our study also showed a negative effect on children's asthma control of adults smoking within the home (particularly mothers for PEF control). Our results are the opposite of those of the recent study by Crombie *et al*, where parental smoking in the home was associated with a reduction in health care contacts for asthma.[11] This discrepancy is probably explained by the difference in the outcomes considered. In the Crombie *et al* study the outcomes were likely to be related to parents' attitudes, in that smoking parents might not give adequate management to children's asthma. In our study asthma outcomes were more objective.

In our study, compliance to treatment and exposure to tobacco smoke were each independently associated with asthma control in multiple logistic regression analyses which also included other possible predictors. The confounding factors investigated in this study were those that have been described as risk factors of the progression of asthma through childhood.[27] However, we were unable to explore fully the possible effects of severely negative life events[28] because there were very few such events.

As children with severe or unstable asthma were not recruited (according to the protocol) and we analysed the data for those who were prescribed inhaled anti-inflammatory drugs, our results are relevant to patients with mild or moderate persistent asthma, who account for a large proportion of asthmatic children. Although our study was carried out in chest specialists' practices, our findings are probably also applicable to general practices.

We conclude that further efforts should be made to maximise the benefit derived from available asthma medication and to improve health outcomes. Parents of asthmatic children should be persuaded not to smoke in the home, and compliance should be improved by ensuring that patients understand the disease and its treatment and by convincing them that it is essential to take medication exactly as prescribed.

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