

Increase in daytime symptoms is a sensitive and specific criterion for predicting corticosteroid-treated exacerbations in a clinical asthma trial

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Summary

Background To determine which diary card variables are the most predictive for administration of additional courses of corticosteroids using the *TRUST* (The Regular Use of Salbutamol Trial) data set.

Methods Logistic regression models were used to identify the extent to which a change in diary card variable affected the odds ratio (OR) for administering a course of oral or increased inhaled corticosteroids. The complete *TRUST* diary card data were used with over 200 000 days of diary card observations from 983 mild to moderate asthmatic subjects.

Results An increase in daytime symptoms of 1–5 U over baseline was associated with an increase in the OR for starting all types of corticosteroids from two- to 60-fold.

Conclusions These results indicate that an increase in daytime symptoms of two or more over baseline strongly predicts the administration of additional corticosteroids. The results have significant implications for both clinical practice and design of clinical trials in asthma.

Keywords asthma, exacerbation, peak expiratory flow, symptom score

Submitted 2 April 2004; revised 2 December 2004; accepted 17 December 2004

Introduction

Exacerbations of asthma are common and they are disruptive to patients. Furthermore the annual costs of asthma to the NHS are high at around £889 million, in terms of drug usage, hospital admissions and GP consultations [1]. Asthma attacks can increase this further, with average costs of treating a patient with an exacerbation of asthma at £381, which is more than three times that for a patient without an attack (£108). Overall, the treatment of patients with attacks consumes more than half of all healthcare costs for asthma even though they represent only one-fifth of the total number of people with asthma [2]. If those patients who are likely to develop a severe exacerbation could be identified early then treatment could be targeted and hospital admissions and other costs associated with an exacerbation reduced.

A variety of methods for identifying exacerbations have been described previously in clinical trials [3–12]. Many of these approaches use the necessity to administer additional corticosteroids as one of the defining criteria for exacerbation, as national and international guidelines for management have recommended early introduction of corticosteroids [13–16]. The definitions of exacerbation used in clinical trials have varied in the emphasis they place on the different diary card variables.

In an attempt to understand which of the diary card variables were most likely to result in a course of additional corticosteroids we have analysed the *TRUST* (The Regular Use of Salbutamol Trial) [1] data set. Additional oral corticosteroids usage was chosen as a surrogate marker for exacerbation as it was felt that patients would only be prescribed oral corticosteroids in response to a significant deterioration of their asthma.

Methods

TRUST was a randomized controlled trial designed to assess the risks and benefits of long-term regular use of salbutamol in mild to moderate asthmatic subjects [1]. A total of 983 patients were randomized to receive salbutamol or placebo and were followed-up for 12 months with an average follow-up of 8.5 months and over 200 000 days of diary card observations. Patients recorded the best of three morning and evening pre-bronchodilator peak expiratory flow (PEF) using a mini-Wright PEF meter (Clement Clarke International, Harlow, UK). Daytime and night-time symptoms were recorded using a six-point scale (Fig. 1), patients also recorded the use of rescue inhaled β_2 -agonists, additional corticosteroid usage, visits to the doctor or hospital for asthma and days off work/school for asthma. There was a 3-week run-in period during which patients completed the asthma diary card whilst taking their usual anti-asthma medication. Data from the run-in period were used to generate the baseline values. The patients, doctors and research nurses were given detailed instructions to administer additional corticosteroids if at least

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Night time symptom score

This should be assessed each morning immediately after awakening. Symptoms are chest tightness, wheezing, breathlessness and cough.

- 0 No symptoms during the night.
- 1 Symptoms on waking but not causing you to wake early.
- 2 Symptoms causing you to wake once or to wake early.
- 3 Symptoms causing you to wake twice or more (including waking early).
- 4 Symptoms causing you to be awake most of the night.
- 5 Symptoms so severe that you did not sleep at all.

Daytime symptom score

This should be assessed each evening, just before going to bed. Symptoms are chest tightness, wheezing, breathlessness and cough.

- 0 No symptoms.
- 1 Symptoms for one short period during the day.
- 2 Symptoms for two or more short periods during the day.
- 3 Symptoms for most of the day, which did not interfere with usual daytime activities.
- 4 Symptoms for most of the day, which did interfere with usual daytime activities.
- 5 Symptoms so severe that you could not perform your usual daytime activities.

Fig. 1. *TRUST* Diary Card Symptom Score.

two of the following criteria were met on two consecutive days: fall in PEF to less than 80% of baseline level; β_2 -agonist usage in 24 h increased by three or more over baseline; and symptom score increased during the day or at night, by two or more over baseline level. For safety and ethical reasons additional corticosteroids were permitted in the absence of two or more diary card criteria only in those cases where there was a clinical need. The details and results of *TRUST* have been reported elsewhere [1]. Using the *TRUST* diary card data set the onset of courses of additional corticosteroid treatment, both oral and inhaled, were identified.

Statistical analysis

Logistic regression models were used to identify the extent to which a change in the diary card variables compared with no change affected the odds ratio (OR) for administering all courses of additional corticosteroids and for identifying oral and inhaled corticosteroids separately. The crude regression model was a univariate model adjusting only for baseline values. The adjusted OR was obtained using a multivariate model that adjusted for age, sex, inhaled steroid level, baseline values and which used a robust 'sandwich' variance estimator taking into account clustering within patient by relaxing the

assumption of independence of observations [17–19]. All data were analysed using the Stata 6 statistical package.

Results

There were 455 courses of oral or increased inhaled corticosteroid treatment during the *TRUST* follow-up. Corticosteroids were started in 17% (78/455) because of an increase in daytime symptoms; 10% (44/455) because of nocturnal symptoms; 7.5% (34/455) because of increase in β_2 -agonist use and they were given in only 2% (11/455) because of a fall in PEF of 20% or more.

The crude and adjusted ORs for starting a course of corticosteroids are shown in Table 1. The relationships between an increase in daytime symptoms, night-time symptoms or rescue β_2 -agonist use and the use of oral corticosteroids were found to be linear (on the log odds scale). The ORs are given for each change in symptoms or amount of rescue β_2 -agonist used compared with no change in Table 1. There was a two-fold increase in the odds of starting a course of oral and inhaled corticosteroids if there was an increase in daytime symptoms of one to five units over baseline (OR 2.1, 95% confidence interval (CI) 1.56–2.87,

Table 1. The effect of diary card variables on the ORs of starting a course of corticosteroids

Diary card variable	Oral corticosteroids		Inhaled corticosteroids	
	Crude OR (95% CI)	Adjusted OR* (95% CI)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Decrease in morning PEF				
5–10% decrease in morning PEF	3.98† (2.0–7.90)	2.46‡ (1.03–5.88)	2.30† (1.72–3.07)	1.41 (0.99–1.99)
10–20% decrease in morning PEF	8.59† (3.81–19.3)	2.40 (0.70–8.21)	4.13† (2.78–6.12)	1.58 (0.92–2.74)
> 20% decrease in morning PEF	23.3† (9.79–55.4)	2.74 (0.63–11.9)	5.22† (2.90–9.39)	1.03 (0.43–2.45)
Decrease in evening PEF				
5–10% decrease in evening PEF	3.86† (1.95–7.66)	2.03 (0.91–4.56)	2.32† (1.75–3.09)	1.35 (0.97–1.87)
10–20% decrease in evening PEF	8.89† (3.92–20.2)	3.1‡ (1.08–8.88)	3.72† (2.46–5.64)	1.26 (0.73–2.16)
> 20% decrease in evening PEF	40.9† (17.9–93.1)	4.85‡ (1.56–20.3)	9.08† (5.25–15.7)	1.93 (0.83–4.49)
Increase in daytime symptoms				
1 U increase daytime symptoms	2.43§ (1.23–4.84)	1.75 (0.77–3.95)	3.97† (2.87–5.48)	2.52† (1.70–3.72)
2 U increase daytime symptoms	11.06† (5.50–22.22)	4.34§ (1.52–12.44)	15.6† (11.0–22.0)	7.18† (4.57–11.3)
3 U increase daytime symptoms	35.25† (16.15–76.95)	10.38† (3.11–34.60)	17.7† (10.2–30.8)	6.29† (3.10–12.8)
4 U increase daytime symptoms	62.31† (18.15–213.97)	7.01‡ (1.08–45.49)	80.9† (43.0–152)	22.71† (10.3–50.1)
5 U increase daytime symptoms	353.24† (99.24–1257)	60.62† (12.78–299)	74.8† (17.8–314)	26.1† (5.68–120)
Increase in night-time symptoms				
1 U increase in night-time symptoms	2.58§ (1.41–4.70)	1.12 (0.54–2.34)	2.83† (2.09–3.83)	1.57‡ (1.08–2.28)
2 U increase in night-time symptoms	5.28† (2.33–11.98)	0.69 (0.21–2.26)	9.77† (6.98–13.7)	3.04† (1.88–4.93)
3 U increase in night-time symptoms	29.34† (12.19–70.67)	1.81 (0.46–7.20)	18.2† (10.4–31.9)	2.93§ (1.53–5.62)
4 U increase in night-time symptoms	138.77† (48.0–401.15)	4.2 (0.73–24.41)	27.0† (8.47–86.0)	2.27 (0.63–8.24)
Increase in rescue β_2 -agonist use				
2–6 puffs increase in rescue β_2 -agonist use	5.42† (2.80–10.50)	1.27 (0.57–2.84)	4.22† (3.02–5.91)	1.11 (0.73–1.67)
6–10 puffs increase in rescue β_2 -agonist use	20.48† (7.98–52.59)	2.15 (0.74–6.29)	6.94† (3.40–14.2)	0.93 (0.42–2.04)

*Adjusted for baseline values, age, sex and clustering within patient. † $P < 0.001$, ‡ $P < 0.05$, § $P < 0.01$.

The ORs compare the odds for the given change in a variable against the odds for no change.

OR, odds ratio; CI, confidence interval; PEF, peak expiratory flow.

$P < 0.001$). This was in marked contrast to the much smaller effects on oral corticosteroid usage of an increase in night-time symptoms (OR 1.15 95% CI 0.79–1.67) or an increase in rescue β_2 -agonist usage (OR 1.23 95% CI 0.91–1.67) which were not significant. While there was a fourfold increase in OR for starting a course of oral corticosteroids with a fall in evening PEF of more than 20% compared with no change in PEF, there was no significant increase in the OR for starting inhaled corticosteroids in response to a decrease in evening PEF (Table 1). There was no significant increase in the odds of starting either oral or inhaled corticosteroids in response to a fall of 20% or more in morning PEF.

Discussion

The results of this analysis indicate that of all the diary card variables an increase in daytime symptoms is strongly predictive of additional oral or increased inhaled corticosteroid usage as a surrogate marker for exacerbation. The original TRUST data were collected in general practice and whilst it would have been useful to have measured inflammatory markers or airways hyper-responsiveness this was not feasible with such a large number of patients recruited in primary care. It was especially interesting to note the relatively weak relationship between night-time symptoms and corticosteroids usage in the regression analysis, particularly with oral corticosteroid usage. This was unexpected since many patients are taught that an increase in nocturnal

symptoms or waking with asthma is one of the earliest signs of deterioration in asthma control, although the evidence base for this recommendation is unclear. While daytime symptoms strongly predicted additional corticosteroid usage there were still many courses of corticosteroids that were started with no associated change in any of the diary card variables. It was surprising how few of the courses of additional corticosteroids were started in response to a fall in morning PEF as this is most often used in the monitoring of asthma control in clinical trials.

An increase in daytime symptoms was slightly less sensitive for predicting the introduction of oral corticosteroids than in predicting exacerbations in which inhaled corticosteroids were given. This suggests that patients may have been starting inhaled corticosteroids in response to daytime symptoms in the absence of other changes, but by contrast they may be starting oral corticosteroids in response to more severe asthma characterized by a change in more than one diary card variable. The CIs were wide for larger increases in daytime symptoms compared with no change and this was probably because there were fewer occasions (and therefore smaller numbers) when there were very large increases in symptoms scores. In spite of this, the ORs are high and very significant supporting the suggestion that large increases in daytime symptoms over baseline are likely to lead to treatment with corticosteroids.

From a clinical perspective, an increase in daytime symptoms can be readily recognized by patients and doctors; it does not require peak flow monitoring and could be used as

a simple and practical way to advise patients to adjust their medication. As PEF measurements contribute minimally to the prediction of an exacerbation, although a fall in evening PEF of 20% or more strongly predicted the use of oral corticosteroids, self-management plans could be simplified and patients may not need to make twice daily PEF measurements and this in turn may improve compliance with asthma monitoring. The results of this analysis provide some evidence base to support the use of the three questions recommended by the RCP for the clinical monitoring of asthma [20, 14].

Our data is consistent with several pieces of previous work that have analysed asthma exacerbations in an attempt to identify the most suitable outcome measures for use in clinical trials [21–24]. For instance, Tattersfield et al. [22] reported that 73% of FACET exacerbations resulted in treatment with oral corticosteroids in response to increasing symptoms rather than a fall in morning PEF.

Chan-Yeung et al. [21] studied 120 patients (adults and children) taking part in a nested case control study of viral exacerbation and 41% of patients experienced an exacerbation. They found that symptoms started to increase 2 days before the first day of exacerbation and that this occurred before the PEF fell. PEF rarely fell by 30% or more from baseline. The authors concluded that a symptom diary identified exacerbations earlier than PEF changes. Shingo et al. [23] investigated the correlation between asthma diary card variables of 1500 patients participating in two 1-year clinical trials. Within patient pairwise correlations of the diary card variables were made. The diary card variables were poorly correlated with one another although all comparisons were significant.

Our results extend the conclusions presented in these earlier reports by analysing over 200 000 observations, in a total of 983 patients with a mean follow-up of 8.5 months compared with studies with much shorter periods of follow-up and may have implications for design of clinical trials. All the patients, doctors and nurses were given the same information on the TRUST definition of an exacerbation and provided with detailed instructions for administration of extra treatment, so there should have been a large measure of consistency. For safety reasons, the definition of an exacerbation also included a 'clinical need for oral corticosteroids' and there may have been some differences in the extent to which the patients, doctors and nurses interpreted this criterion. The data do not allow for the differences to be examined, although the logistic regression models take clustering within patients into account. Whilst further comparisons between the nurse and doctor may be interesting it is not possible to analyse the data in this context in the present study design.

Even though health professionals and patients were given clear guidelines for starting additional corticosteroids the results of this analysis have identified that a change in some diary card variables was more likely to result in treatment with additional corticosteroids than others and that many patients appear to start additional corticosteroids without any significant apparent change in their asthma. While this could be interpreted as inappropriate use of glucocorticoids, it could equally be caused by doctors or patients starting steroids at the first sign of a clinical deterioration, which they have learnt from experience will result in an exacerbation, before the subjective and objective symptoms and signs satisfied trial definitions.

Diary card variables are poorly correlated with one another and a change in one variable may not be accompanied by a change in another variable. A measure with fewer variables, such as the use of a daytime symptom score, may be more suitable than a composite measure. The inclusion of morning PEF may not justify the additional work expected from the patients and may result in reduced compliance with diary card monitoring. A composite measure of outcome in asthma control, comprising several different variables, is best utilized when the components are well correlated, and symptoms of disease are more genuinely one-dimensional. Future work should test the hypothesis that daytime symptom scores alone could identify asthma exacerbations in prospective clinical trials and for routine asthma management in comparison with more complex definitions of an exacerbation.

Acknowledgements

Sarah Dennis received a grant from the Guy's and St Thomas' Charitable Foundation. Prof. Tak Lee is funded by Asthma UK. *TRUST* was funded by the Medical Research Council, UK. The authors would like to thank Prof. N. Barnes, Prof. T. W. Meade, Mr C. Frost and Dr M. Vickers for their advice during the course of this project.

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