Peak expiratory flow analysis in workers exposed to detergent enzymes

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Aims	To study serial peak expiratory flow (PEF) responses in a group of symptomatic detergent enzyme-exposed workers.
Methods	Workers were recruited from a biological detergent formulating and packaging company. Those with occupational asthma symptoms and/or specific IgE to a detergent enzyme were asked to complete 2 hourly PEF measurements for 4 weeks. Outputs from the Oasys program (Oasys score, rest–work score and rest–work difference in diurnal variation) assessed PEF response. These were then related to the levels of sensitization and current occupational exposure to detergent enzymes.
Results	In all, 67/72 workers returned PEF records; 97% were able to return a record with at least four readings per day and 87% at least 3 weeks in length. Of total, 79% ($n = 27$) of those with a final diagnosis of occupational asthma had peak flow records confirming the disease using Oasys. PEF response was similar in those with high, medium and low levels of exposures and those with negative, low–moderate and high specific IgE levels.
Conclusions	The Oasys program is a sensitive tool for the diagnosis of detergent enzyme occupational asthma, but the levels of exposure and specific IgE sensitization to enzymes do not affect the magnitude of PEF response in symptomatic workers.
Key words	Detergent enzymes; Oasys; occupational asthma; peak expiratory flow.

Introduction

Serial measurement of peak expiratory flow (PEF) is recommended in the objective confirmation of occupational asthma [1] since the technique, if appropriately analysed, has been shown to be both sensitive and specific for identifying patients with the disease [2,3,4]. Gannon *et al.* [5] developed a computer program called Oasys-2 to use in the analysis of serial PEF measurements that has a sensitivity of 75% and specificity of 94% against independently diagnosed cases of occupational asthma referred to a specialist clinic. The program allows data entry of serial PEF measurements, produces a graph showing maximum, mean and minimum daily values and scores of how likely the recorded data reflects work-related asthma using discriminant analysis. For the Oasys score, the system analyses 'complexes' (a complex is a rest–work–rest period or a work–rest–work period) [5, 6]. The Oasys score requires at least three complexes of data (this equates to ∼3 weeks in a 9–5 Monday to Friday worker), ≥4 readings per day (for 75% of the record) and ≥3 consecutive workdays in any work period (for 75% of the record) to give optimal sensitivity and specificity for the diagnosis [7]. The Oasys program also calculates a rest–work score based on 'day interpreted' records, a feature of Oasys [6]. This has previously been found to have a sensitivity of up to 70% and specificity of 95% for the diagnosis of occupational asthma [8] based on the upper 95% confidence limit for grain-exposed non-occupational asthmatics. In the same project, a difference of 7.2% between rest diurnal variation and work diurnal variation was found to be the upper 95% confidence limit, producing a sensitivity of 27%. As some institutions analyse whether diurnal variation increases on workdays compared to rest in the diagnosis of occupational asthma [9, 10], this output has been included to compare with the Oasys and rest–work scores.

The original validation of the Oasys score was conducted using records from workers mostly exposed to low molecular weight agents. We now present a further validation study in a single workplace with exposures to

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high molecular weight occupational asthmagens during an investigation of the largest recorded outbreak of enzyme-induced asthma. The relationships between the degree of sensitization to an occupational antigen such as detergent enzymes, the level of exposure and the magnitude of PEF changes within a workday or over a working week have not been reported previously.

Methods

Workers were recruited from two cross-sectional surveys, in 1998 and 2000, of a biological detergent formulating and packaging company. The factory used encapsulated proteases (from 1985), amylase (1990) and cellulase (1996). Workers who had reported symptoms suggestive of occupational asthma on a survey questionnaire and/or had evidence of a positive skin prick test and/or specific IgE to one or more detergent enzymes (savinase, termamyl or cellulase) were included. Those who fulfilled these criteria were offered a clinic appointment with a specialist occupational asthma team and asked to keep serial PEF records. A final clinical diagnosis of occupational asthma, occupational rhinitis or non-occupational asthma was made by an experienced occupational lung disease clinician. This was based on the questionnaire responses, a full history and clinical examination, lung function testing, visual analysis of PEF plots (not using Oasys), results of specific IgE measurements and in some cases specific inhalation challenge testing with enzymes. Those found to have allergy to the enzymes encountered at work were diagnosed as occupational asthma (or rhinitis depending on symptoms) and those with other causes were diagnosed as non-occupational asthma. Oasys plots of the serial PEF measurements were not available at the time of diagnosis.

Workers were asked to take PEF readings every 2 h from waking to sleeping, on days at work and away from work, for a total of 4 weeks. They were instructed by a specialist respiratory nurse on how to take readings using a Mini-Wright non-linear peak flow meter and told at each measurement time to take at least three readings with at least two being reproducible (within 10 l/min). Those taking treatment for their asthma were asked to take it at similar times each day. All workers were asked to write down their work times and readings on the specially provided occupational PEF forms.

All subjects were anonymized by assigning a new identification number. If workers had completed >1 PEF record, the one closest to the time of the final diagnosis was the one chosen to be put through the Oasys program. The East Birmingham Ethics committee, UK, approved this project without requiring patient consent as all data were anonymized.

Other data were then collected for each worker from either a central database or from the clinical notes. These included

1. Specific IgE measurements nearest to the date of the peak flow record. A positive IgE was defined as >2% radioallergosorbent test (RAST) binding. The results were also split into categories: 'mild positive' (2–10% binding), 'moderate positive' (≥10 to <20%) and 'high positive' (≥20% binding).
2. Skin prick test results to common aeroallergens (cat dander, grass pollen and *Deratophogoides pteronyssinus*; Allergopharma, Reinbeck, Germany) and the specific enzymes (cellulose, termamyl and savinase) used in the factory (solutions of 1 mg/ml produced from the factory enzymes). A positive skin prick test was defined as one producing a mean wheal diameter of >3 mm wheal above the response to a saline negative control.
3. Enzyme exposure level: Job titles were classified into categories of high, medium/intermittent or low exposures based on a qualitative assessment of tasks and work areas complemented by direct measurements of airborne enzyme. The highest exposures were judged to occur in certain packing tasks followed by production jobs and then distribution work. Employees in laboratories had lower exposures and office staff the lowest. Factory engineers had intermittently high exposures. The job title at the time of completing the PEF record was used.
4. Treatment for asthma: Workers were categorized as either currently taking regular inhaled corticosteroids or not at the time of making their serial PEF measurements.
5. Basic demographic data: Smoking history (current, ex-smoker or never smoker), age, sex and atopic status. Atopy was defined by a positive skin prick test to a common aeroallergen.

Records were linearized [11], day interpreted [6], plotted and scored by the computer program Oasys Utilities which uses the same discriminant analysis as Oasys-2 [6] to compute a score between 1 and 4 indicating the probability of occupational asthma. Figure 1 shows a PEF record that has been plotted in Oasys Utilities showing occupational asthma. PEF records were assessed for optimal data quantity which has been previously defined for the Oasys score as ≥4 readings per day, three complexes of data [5] and three consecutive workdays in any work period [7]. The following measures of PEF variability were also analysed:

1. Work–rest difference in diurnal variation (DV): This was calculated from the difference in mean DV on rest days from the mean DV on workdays. The outcome was then grouped into those with a work DV − rest DV >7.2% and those without.
2. Oasys score: The workers were then grouped into those with Oasys scores ± 2.51.
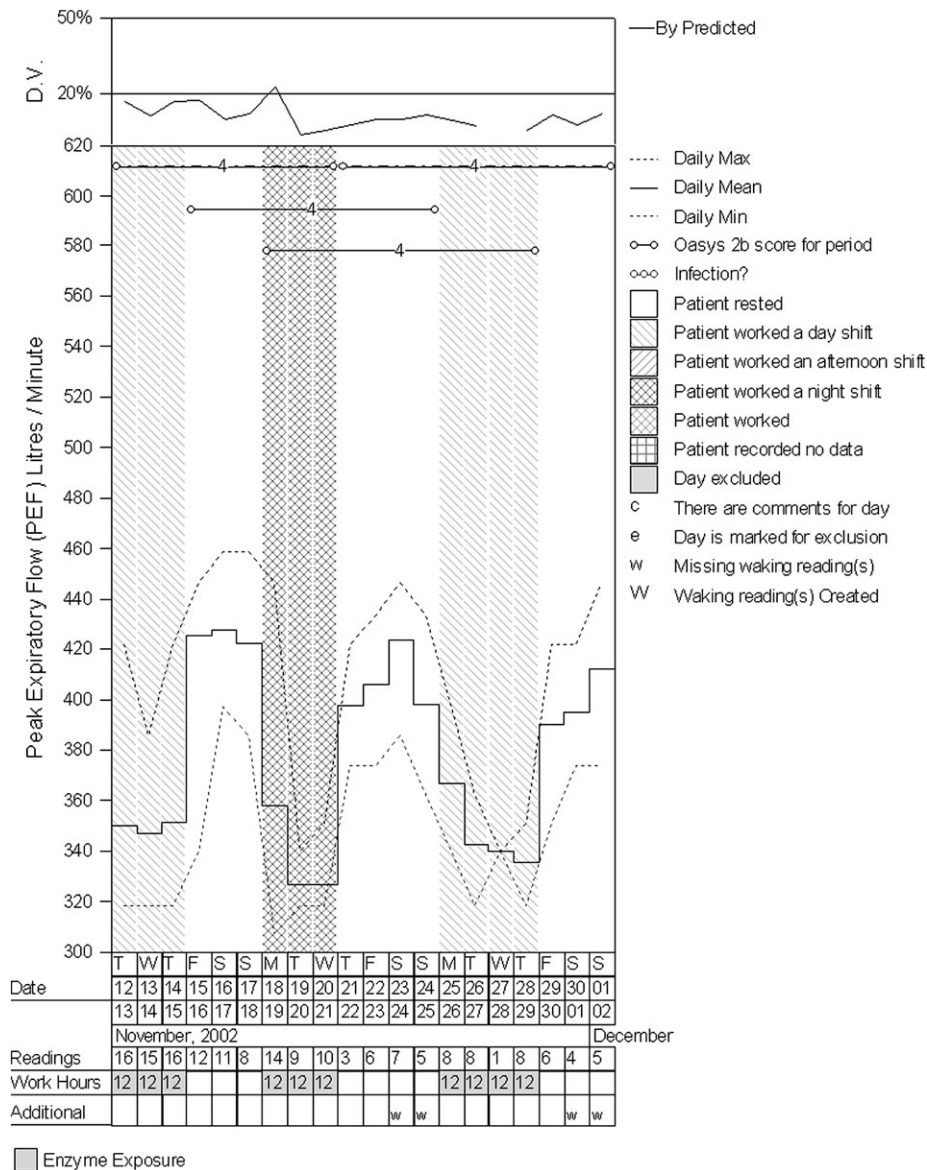3. The mean rest PEF minus the mean work PEF on Oasys day-interpreted data. Data were categorized

Figure 1. Worker with a positive peak flow record and final diagnosis of occupational asthma. The top part of the chart shows the mean diurnal variation (DV) for each day. The middle of the chart shows the maximum, mean and minimum peak flow for each day. The work periods are the shaded areas (diagonal bars, morning shift; cross-hatched, night shift) and the rest periods are blank. The lines containing numbers in this part of the chart are scores for complexes (four complexes in total for this record). The black continuous line is the mean PEF, the upper line the maximum PEF and lower the minimum PEF for each day. At the bottom of the record are the days and dates of the record. The Oasys score of this record is 4.00, mean rest–work score is 68 l/min and predicted PEF is 612 l/min. This worker had 39% specific IgE binding to savinase and worked as a packer in a high exposure area.

into those with a rest–work score of ±16 l/min to define probable occupational asthma.

The Mann–Whitney *U*-test was used to compare PEF indices with smoking, atopy, predicted PEF and treatment; analysis of covariance (ANCOVA) used to investigate the effects of exposure and IgE level on PEF outcomes while controlling for other confounders such as age, smoking, inhaled corticosteroid use and atopic status. The sensitivity and specificity of diagnostic test have also been evaluated. SPSS version 15 has been used to carry out all statistics.

Results

A total of 67 peak flow records were available from 72 workers who were originally recruited, with 66 including both work and rest days. Ninety-seven per cent of returned PEFs had ≥ 4 readings/day (for 75% of record), 87% had ≥ 3 complexes in length (~ 3 weeks of recordings) and 46% had ≥ 3 days at work in each work period (for 75% of the record). Thirty-nine per cent were optimal for all three data quantity criteria. The mean age of the employees was 36.5 years [standard deviation (SD) = 9.1], 80% were male, 48% atopic, 53% current smokers and 30% using

inhaled corticosteroids at the time of completing their PEF record. Eighty-seven per cent had serum specific IgE antibodies and 96% had a positive specific skin prick test to at least one detergent enzyme; 97% reported work-related symptoms on their questionnaire.

Table 1 shows the percentage of workers diagnosed with occupational asthma by Oasys compared to the independent clinical diagnosis or other investigations. Eight out of thirty-five workers were clinically diagnosed with occupational asthma by the independent physician but had scores of <2.51 on Oasys. Three of these were confirmed as having occupational asthma by specific bronchial challenge tests.

Table 2 shows differences in PEF outcomes between some of the demographic groups. There were significant differences in Oasys score, rest–work score and work–rest diurnal variation between those who were atopic and non-atopic. Rest–work score was also statistically significantly affected by taking inhaled corticosteroid treatment (those taking steroids had higher PEF scores).

Table 3 shows the means and SDs for the three Oasys program PEF measures when distributed across three exposure levels and three specific IgE RAST levels with their corresponding significance using ANCOVA (correcting for confounders of age, atopy, smoking and inhaled corticosteroid use). There was no difference in Oasys scores between those with low, medium/intermittent and high enzyme exposure or those with a negative, low/moderate and high specific IgE RAST level.

Discussion

We have found that Oasys has a high sensitivity when compared to independent confirmatory tests of specific IgE and questionnaire data (with no other final diagnosis). It diagnosed 79% of those with a positive IgE and work-related asthmatic symptoms on the questionnaire who had a clinical diagnosis of occupational asthma. It also confirmed a diagnosis of occupational asthma in 64% of workers with a questionnaire showing work-related asthmatic symptoms or specific IgE to at least one of the detergent enzymes. Specificity could not be calculated as records from unexposed asthmatic workers were not obtained, but previous studies of non-occupational asthmatics have shown that an Oasys score of >2.50 has a specificity of 94% [5].

The independent clinician did not diagnose occupational asthma in 20 of those identified by Oasys as having work-related changes in PEF a characteristic of occupational asthma. Four of these had no clinical disease diagnosed, three had no final diagnosis (lost to follow-up) and the rest had a clinical diagnosis of occupational rhinitis, with two being confirmed through specific bronchial challenge testing. Some evaluators may require large deteriorations in PEF on workdays compared to rest days to diagnose occupational asthma [12], similar to the requirements of a 20% fall in forced expiratory volume in 1 s from specific inhalation challenge. Among those with occupational rhinitis, the mean difference in rest–work PEF was 25.6 l/min (SD 17.4) compared with 60.9 l/min (SD 33.0) in those with occupational asthma. In asymptomatic workers exposed to high levels of grain dust, the 95% confidence interval for mean rest–work difference in PEF is 16 l/min [8], suggesting that at least the 25.6 l/min is outside the normal range. Of the eight workers who had an Oasys score <2.51 but a clinical diagnosis of occupational asthma, half had borderline Oasys scores.

Exposure level was not related to any measures of PEF response in the working environment. This may have been due to a very small number of workers being in low exposure jobs. In our opinion, it is likely that those with more severe asthmatic reactions could not tolerate regular exposure and therefore reduced their exposures.

Although workers with the highest specific IgE levels generally had the lowest PEF response, the correlation was not statistically significant. The lack of a representative sample of non-sensitized workers in this study prevents a comparison of sensitized with non-sensitized workers. We also found no interaction effects between exposure, specific IgE and PEF response.

Most of the records in this study achieved optimal readings per day and length of the record. A diagnostic sensitivity of 79% was achieved despite many not having three consecutive days in each work period, a requirement for optimal sensitivity in workers exposed to low molecular weight agents [7]. This suggests that three consecutive workdays are not a requirement when there are large reactions to high molecular weight agents.

Table 1. Clinical diagnosis versus Oasys scores

Clinical diagnosis/investigation	n	Oasys score ≥2.51, n (%)	Rest–work score ≥16 l/min, n (%)	Work DV − rest DV >7.2%, n (%)
Positive specific IgE and work-related asthmatic questionnaire	34	26 (76)	27 (79)	8 (24)
Occupational rhinitis	19	7 (37)	8 (42)	0
Non-occupational asthma	1	0	0	0
Normal	6	4 (67)	3 (50)	0
No diagnosis made	5	3 (60)	3 (60)	1 (20)

Table 2. Confounding factors and PEF outcome

	Mean Oasys score (SD)	Mean rest–work score (SD)	Mean work–rest DV (SD)
Atopic			
Yes	3.1 (0.8)	44.9 (36.8)	5.0 (6.3)
No	2.7 (0.9)*	27.2 (32.4)*	1.6 (6.6)**
Smoker			
Yes	3.1 (0.8)	40.1 (35.0)	2.9 (6.3)
No	2.7 (1.0)	30.6 (35.9)	3.7 (7.1)
Inhaled corticosteroids			
Yes	3.23 (0.67)	48.8 (30.4)	4.16 (8.31)
No	2.78 (0.95)	30.5 (36.3)*	2.91 (5.88)

*$P < 0.05$, **$P < 0.01$.

Table 3. Parameters of PEF record by exposure category (from job title) and specific IgE RAST level

	Mean Oasys score (SD)	Mean rest–work score (SD)	Mean work–rest DV (SD)
Low exposure ($n = 7$)	2.8 (1.0)	41.6 (45.5)	4.4 (9.2)
Medium/intermittent exposure ($n = 11$)	2.9 (0.8)	31.0 (23.6)	−0.3 (7.0)
High exposure ($n = 49$)	2.9 (0.9)	36.0 (36.7)	4.0 (6.0)
Negative specific IgE ($n = 9$)	3.1 (0.7)	39.4 (35.8)	4.4 (8.1)
Low/moderate positive ($n = 13$)	3.2 (0.9)	45.4 (37.0)	2.0 (4.7)
High positive ($n = 45$)	2.7 (1.0)	32.2 (35.2)	3.5 (6.8)

The interaction between exposure level (by job title) and specific IgE level on PEF response (using mean rest–work score) was analysed using an ANCOVA (correcting for confounders of age, atopy, smoking and inhaled corticosteroid treatment). No interactions were seen, $F = 0.122$, $P = 0.310$, $r^2 = 0.20$.

PEF records (plotted in a different program to Oasys) were available to the independent clinician making it possible that the PEF record influenced the final diagnosis. However, Oasys identified more records suggesting occupational asthma than the independent physician, indicating that different criteria were used for diagnosing occupational asthma from PEF records by the clinician.

Exposure levels were subjectively assessed for each job title rather than relying on air level measurements. In previous work by Cullinan *et al.* [13], exposure, as assessed by job title, was related to the degree of sensitization in these workers, suggesting that this method of exposure categorization is still useful. The peak flows may have been sensitive to daily changes in enzyme levels which this categorization does not allow for.

Our study found no relationship between exposure and PEF response. This is similar to a cross-sectional study of laboratory animal workers by Hollander *et al.* who also found no relationship to rat urinary levels. In their study,

PEF response was analysed by using the maximum PEF averaged over all working days with laboratory animal exposure minus the maximum PEF averaged over all working days without laboratory animal exposure, and exposure was divided into low, medium or high rat urinary aeroallergen levels [14].

In a previous study of this detergent enzyme worker population, exposure, as assessed by job title, was related to the degree of sensitization [13]. The lower PEF responses in highly sensitized individuals could be due to some of these workers being moved to a lower exposure job before the PEF record was carried out, therefore reducing the PEF response. Alternatively, it may just be that PEF response is similar no matter how sensitized an individual is. Our findings do not concord with Bryant *et al.* [15] who found that the level of specific IgE and nonspecific reactivity predict the airway response to grass pollen and house dust mite when asthmatics, rhinitics and healthy atopics are included.

In conclusion, this study indicates that analysis of serial PEF measurements in a representative sample of workers is sensitive in the detection of occupational asthma associated with specific IgE antibody production in a detergent factory.

Key points

- Serial PEF measurements with optimum readings per day and length of record are achievable in workers exposed to detergent enzymes.
- Serial peak flow analysis by the Oasys program has a sensitivity of 79% for the diagnosis of occupational asthma in detergent enzyme workers.
- Exposure level and specific IgE level to detergent enzymes are not associated with the magnitude of PEF response in symptomatic workers.

Conflicts of interest

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