The effects of nedocromil sodium on the response to grain dust in West Australian grain workers

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Abstract

Seasonal grain workers in Western Australia who develop respiratory symptoms after exposure to grain dust develop concomitant changes in lung function and bronchial responsiveness to methacholine. The mechanisms underlying these changes are not known. A detailed study was undertaken of seasonal grain workers in Western Australia to evaluate the effect of nedocromil sodium (Fisons, United Kingdom) on these changes to see if they could be prevented by this drug. Forty seven subjects participated. Symptoms and forced expiratory volume in one second (FEV₁) were recorded before the study and before, during, and after each working shift, and bronchial responsiveness to methacholine was measured at the beginning and end of the study. Twenty three subjects received nedocromil and 22 received a placebo in a double blind design; there was no difference in baseline characteristics between the two groups. At the end of the study, no differences were found between the nedocromil and placebo groups in the prevalence of symptoms or development of new symptoms during the study. The drug had no effect on changes in methacholine PD₂₀ or FEV₁. As in previous studies, new symptoms developing during the season were more common in atopic subjects and were associated with a fall in methacholine PD₂₀. It is concluded that nedocromil has no effect on the development of new symptoms in grain workers. The mechanisms underlying these symptoms require further study.

Grain dust has both acute and long term effects on the airways.¹⁻⁵ A few affected subjects develop allergic asthma (due to durum wheat,⁶ storage mites,⁷ or unknown allergens⁸) but in general the mechanisms

responsible for these effects have not been established. Studies in seasonal workers in the Western Australia grain industry have shown that symptoms developing in subjects newly exposed to grain are associated with a fall in forced expiratory volume in one second (FEV₁) and increased bronchial responsiveness. These changes appear soon after exposure at work and do not result from the presence of asthma, which is rare.^{9,10} Bronchial responsiveness is also increased in grain workers without allergic asthma.¹¹ These observations suggest that inflammation of airways, perhaps implicating mast cells, may contribute to the development of obstruction of airways in grain workers.

It is difficult to obtain direct evidence of a contribution from mast cells and inflammatory processes in responses of airways to natural environmental exposures. The response to drugs which suppress release of inflammatory mediators may provide indirect evidence for these mechanisms. The present study reports the effects of nedocromil sodium (Fisons, Loughborough, United Kingdom) on the respiratory response to grain dust in Western Australian grain workers. Nedocromil is a stabilising agent for mast cells, with similar effects to sodium cromoglycate.¹² It is effective in the prevention of allergen induced bronchospasm and in the treatment of asthma.^{13,14} The effects of this drug have been compared with a placebo in a double blind comparison in 47 employees of a grain depot during the 1986-7 grain season.

Subjects and methods

SUBJECTS AND WORKPLACE

Workers were studied at one grain depot in central Western Australia. The depot is a major inland transfer point for grain grown in the central Western Australian wheatbelt. Most grain arrives by rail and is transferred through conveyors to temporary storage in concrete silos before being transferred to other railway wagons for transport to the docks. Peak activity at the depot is from November to January. During this time, the small permanent staff is augmented by workers employed for the season.

Seventeen permanent staff and 30 seasonal staff volunteered to participate. This represented 94% of

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the seasonal workers and 59% of the permanent workforce employed at the plant for the duration of the study. No details were available on the 12 permanent workers and two seasonal workers who declined to take part.

Workers were employed in several different locations in the plant (see table 1). Most moved from job to job within the plant daily or weekly; only supervisory staff remained in the same job for the duration of the study. At the peak of the season employees worked a day shift (7.00 am to 6.00 pm) or a night shift (7.00 pm to 3.00 am). A week of days preceded a week of nights. Informed consent for the study was obtained in writing from each participant and the study was approved by the human rights committee of the Sir Charles Gairdner Hospital.

METHODS

At the beginning of the study, subjects were asked to complete a baseline questionnaire, and pulmonary function and bronchial responsiveness to methacholine were measured. Subjects were randomly assigned to receive either nedocromil or placebo from a metered dose inhaler. Subjects reported to the survey team three times during each shift throughout the study. On each occasion, symptoms arising since the last visit were recorded, spirometry was performed, and two puffs of nedocromil or placebo were administered in a double blind design. Bronchial responsiveness was measured at the beginning of the study, after four weeks, and at the end of the study. The study was planned to last six weeks.

QUESTIONNAIRE

The questionnaire, modified from a Medical Research Council version, with additional questions relating to occupational exposure and to allergic

symptoms, was presented to participants by trained interviewers to record symptoms occurring before the start of the study. Smoking and occupational histories were also recorded. Current smokers were defined as those who had smoked at least one cigarette a day for more than one year, and ex-smokers were defined as those who had smoked this much in the past but had not smoked for one year before the start of the study. Symptoms of cough, wheeze, breathlessness, and chest tightness were recorded on each subject at the beginning, middle, and end of each shift. These were graded from none (0) to severe (3). Unusual symptoms or adverse effects of the drug were recorded at the same time. Symptoms recorded in the 12 hours after challenge with methacholine were not included in the analysis.

SPIROMETRY

Forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured on one of three dry bellows spirometers (Vitalograph, Bucks, United Kingdom). Three recordings within 5% or 100 ml were obtained from each subject at the start of the study and at each visit to the survey team during each shift at the same time as their symptoms were recorded. The spirometers were calibrated at regular intervals using a one litre calibrating syringe, and each subject was always tested on the same spirometer.

BRONCHIAL RESPONSIVENESS TO METHACHOLINE

Bronchial responsiveness to methacholine was measured in 46 subjects by the method of Yan *et al.*¹⁵ Methacholine was administered in increasing concentrations from a deVilbiss No 40 hand held glass nebuliser (deVilbiss, Somerset, Pa, USA), until the FEV₁ had fallen by 20% of the lowest value after saline control inhalation (methacholine PD₂₀ is the dose provoking the 20% fall) or until the maximum dose of 100.8 µmol methacholine (representing a concentration of 400 mg/ml) had been reached. Bronchoconstriction was reversed with a salbutamol inhaler. The PD₂₀ was derived by linear interpolation.

SKIN PRICK TESTS

Skin prick tests were performed according to the method described by Pepys.¹⁶ Extracts of common domestic inhalant allergens were used to detect atopic subjects who were defined as having one or more positive skin tests (> 3 mm > negative control) to one of the following allergens: *Dermatophagoides pteronyssinus*, 1% w/v; *Dermatophagoides farinae*, 1:55 w/v; rye grass pollen extract, 1:10 w/v; mixed moulds (*Aspergillus fumigatus*, *Alternaria*); cat epithelium dander 10% w/v (Hollister Stier). Histamine (10 µg/ml) was used as a positive control.

Table 1 Job locations and dust concentrations

	No of samples	Grain dust concentrations
		Mean dust concentrations mg/m ³ (range)
Grid and loading:	23	3.72 (0.46–62.15)
Direct loading and unloading rail wagons and trucks		
Under rail:	6	2.42 (0.62–7.0)
Basement, direct unloading rail wagons		
Over cells:	6	2.16 (0.55–5.75)
Top floor conveyers		
Capstans:	10	1.74 (0.16–14.21)
Loading and unloading; less close than Grid		
Shed storage:	6	8.02 (3.63–30.01)
Bulldozer handling of floor stored grain		
Control areas:	6	0.79 (0.34–3.24)
Scattered throughout plant		

ADMINISTRATION OF DRUGS

Nedocromil or placebo was administered to each subject from a metered dose inhaler delivering 2 mg of nedocromil at each actuation; 4 mg were administered at each visit by a member of the survey team. Drugs were given three times during each shift, but were not given on the days when the subjects were not at work.

DUST EXPOSURE

Individual dust exposure was measured using personal samplers supplied by the Department of Occupational Safety and Health of the Government of Western Australia. Preweighed 0.5 µ PVC filters were used in 37 mm single hole samplers attached to a Dupont 2500A constant flow pump. Filters were weighed after equilibration in the laboratory. Measurements were made on 61 shifts, representing most jobs in the plant, to obtain average dust concentrations over the period of the shift, or part of the shift, if the dust concentration was very high (minimum recording time two hours). At each visit to the survey team, subjects were asked to record their estimated dust exposure since their last visit to provide a subjective estimate of intensity. The response was graded from 1 (no dust) to 5 (very high dust concentrations).

STATISTICAL METHODS

Data were entered onto computer files and manually checked against the originals. Both parametric and non-parametric methods were used to analyse the results, and methacholine PD₂₀ values were logarithmically transformed for analysis. Measurements of lung function were compared using Student's *t* test. Analysis of variance was carried out for changes in FEV₁ using subjects as a grouping factor and day or night and exposure levels as within factors, and also using subjects as a grouping factor and day or night and day of the week as within factors. Symptom scores were compared by Mann-Whitney U tests.

Results

Forty seven subjects—17 permanent and 30 seasonal workers—agreed to participate in the study; 24 subjects were randomly allocated to receive nedocromil and 23 subjects to receive placebo. The groups were evenly matched in age, initial lung function, smoking history, atopic state, and methacholine PD₂₀ (table 2).

Two subjects withdrew after only one day of treatment and were excluded from the analysis, leaving 23 in the nedocromil treated group and 22 in the placebo group. The subject taking nedocromil withdrew because of nausea, and the subject taking placebo withdrew because of cough and dyspnoea.

Table 2 Characteristics of subjects

	Nedocromil group	Placebo group
No of subjects	24	23
Mean age (y) (range)	28.1 (17–56)	27.3 (17–51)
Smoking habit:		
Never smoked	10	7
Ex-smoker	0	4
Current smoker	14	12
Atopic	9	12
Initial FEV ₁ (° predicted) (range)	88.4 (61.9–109)	96.2 (73.0–115)
Initial FVC (° predicted) (range)	96.7 (71.0–114)	101.4 (72.9–127)
Methacholine PD ₂₀ (mean baseline; µmol)	22.5	22.2

SYMPTOMS

Table 3 shows the prevalence and type of symptoms reported at any time during the study. Cough was the commonest symptom reported on a daily basis; other symptoms were less frequent. Mean symptom scores were low, showing that symptoms were reported by only a few subjects and were almost invariably graded as mild. There was no significant difference between treated and placebo groups in the prevalence of symptoms or symptom scores. Many of the symptoms that were reported had been recorded by the subjects in the initial questionnaire and could not be specifically related to exposure to grain dust. Table 4 shows symptoms not reported on the initial questionnaire. Fifteen subjects reported such new symptoms, with cough again the most frequent. New symptoms were more common in seasonal workers (12/28) than permanent workers (3/17) but this difference did not reach the 5% level of significance. There was no difference in the prevalence of symptoms between nedocromil and placebo treated groups. New symptoms were significantly more likely to occur in atopic subjects ($\chi^2 = 4.5$, $p < 0.05$) and in subjects with a greater than twofold fall in bronchial responsiveness ($\chi^2 = 9.504$, $p < 0.01$) but were not associated with cigarette smoking.

LUNG FUNCTION

Mean FEV₁ fell over the course of the study by 100 ml in the nedocromil treated group and 30 ml in the placebo treated group. Mean FVC fell by 80 ml in the

Table 3 Prevalence of respiratory symptoms during study

	Nedocromil group (n = 23)		Placebo group (n = 22)	
	Prevalence (%)	Mean symptom score	Prevalence (%)	Mean symptom score
Cough	60.9	0.34	47.6	0.20
Wheeze	13.0	0.01	0	0
Dyspnoea	8.7	0.01	4.8	0.04
Chest tightness	8.7	0.01	4.8	0.002

Table 4 New respiratory symptoms not reported at initial survey

	Nedocromil group (n = 9)	Placebo group (n = 6)
Cough (No of subjects)	8	5
Wheeze (No of subjects)	2	0
Dyspnoea (No of subjects)	1	0
Chest tightness (No of subjects)	1	0

nedocromil group and 300 ml in the placebo group. The differences between the start and finish of the study and between nedocromil and placebo treated groups were not significantly different.

Table 5 shows the shift related change in FEV₁ (Δ FEV₁). No difference was found between nedocromil and placebo treated groups. During the day shift, however, FEV₁ rose significantly in both groups and fell significantly during the night shift in both groups. The difference between changes in FEV₁ for days and nights was highly significant. There was no effect of the working week after allowing for the effect of time of day. Only one subject showed a consistent daytime fall in FEV₁. No correlation was found between symptom scores and Δ FEV₁ for each subject.

BRONCHIAL RESPONSIVENESS TO METHACHOLINE

Methacholine PD₂₀ fell by 6.9 μ mol in the nedocromil treated group and 2.3 μ mol in the placebo group over the period of the study. This difference was not statistically significant. There was no overall correlation between change in methacholine PD₂₀ and symptom scores. Sixteen subjects, however, had a greater than twofold fall in methacholine PD₂₀ during the study period, of whom 10 had described new symptoms. This association between new symptoms and PD₂₀ was significant ($p < 0.01$) and in these 10 subjects mean PD₂₀ fell from 18.4 μ mol to 5.64 μ mol.

EXPOSURE TO GRAIN DUST

Table 1 shows the mean and range of recorded dust exposure concentrations from 62 samples. Ten recordings (16.1%) were greater than 10 mg/m³ and

14 (22.6%) were between 5 mg/m³ and 10 mg/m³. Jobs with the highest dust concentrations were storage sheds and direct loading or unloading, but within jobs there was a large range of dust exposures.

Because the variability within jobs was so great, self reported dust exposure concentrations rather than job exposures were used to study correlations with lung function and symptoms. The correlation between self reported dust exposure concentrations and recorded dust concentrations was significant ($r = 0.526$, $p < 0.01$; fig 1).

RELATION BETWEEN EXPOSURE TO DUST, LUNG FUNCTION, AND SYMPTOMS

Figure 2 shows the prevalence of symptoms at each level of exposure to grain dust. No correlation existed between dust concentrations and the prevalence of symptoms or symptom scores ($r = 0.06$), in either nedocromil or placebo group. Dust exposure levels were not correlated with FEV₁ for the day shift ($r = 0.04$) or the night shift ($r = 0.01$).

EFFECTS OF ATOPY AND SMOKING

There was no association between symptom scores and atopy within each treatment group or for the group as a whole ($\chi^2 = 2.16$, $p > 0.05$). As described

Figure 1 Relation between self reported and measured dust exposure concentrations.

Table 5 Shift related change in FEV₁

	Nedocromil group FEV ₁ (l) (SD)	Placebo group FEV ₁ (l) (SD)
Overall mean change	-0.004 (0.075)	+0.031 (0.140)
Day shift only	+0.115 (0.080)	+0.121 (0.121)
Night shift only	-0.140 (0.110)	-0.145 (0.144)
Day shift (day one of week)	+0.077 (0.167)	+0.141 (0.098)
Day shift (day five of week)	+0.151 (0.139)	+0.108 (0.169)
Night shift (day one of week)	-0.142 (0.196)	-0.136 (0.153)
Night shift (day five of week)	-0.095 (0.109)	-0.140 (0.159)

Figure 2 Relation between self reported dust exposure concentrations and prevalence of symptoms.

above, however, subjects with new symptoms were more likely to be atopic. Smoking was not related to symptom scores or to change in PD_{20} . There was an association between shift related change in FEV_1 and increased smoking in pack-years but only for the day shift ($r=0.31$, $p=0.04$) and it should be noted that the same workers did both day and night shifts at different times and there was no evidence of association during the night shift.

Discussion

The present study confirms the results of previous surveys of West Australian grain workers.^{9,10} Those who developed symptoms for the first time during the season of maximum exposure to grain were more likely to be atopic and showed a significant fall in methacholine PD_{20} . There was no change in FEV_1 during the period of this study and no specifically shift related changes in FEV_1 . The observed differences between changes in FEV_1 during the day and those during the night are likely to be due to the normal diurnal variation of airway calibre.¹⁷

The overall level of symptoms reported in this study was low, despite concentrations of grain dust comparable with those of other surveys in which symptoms and changes in lung function were more frequent.^{3,17} This may be because of differences in the grain itself, or to differences in working conditions. It is also possible that the period of exposure to grain in this study was too short to allow changes in lung function to develop, although in this and previous studies of seasonal grain workers symptoms and changes in bronchial reactivity occurred early rather than developing cumulatively over the course of the season.

Nedocromil had no effect on the overall prevalence of symptoms, or on the development of new symptoms. There was no effect on changes in PD_{20} , FEV_1 , or FEV_1 over a shift.

The mode of action of nedocromil is not precisely known. In primates it is a potent inhibitor of mast cells,¹² it blocks antigen challenge and asthma induced by exercise, and is effective in the treatment of asthma.^{13,14,18} It also inhibits bronchoconstriction induced by sulphur dioxide and bradykinin but has no effect on cough and bronchoconstriction induced by capsaicin.¹⁹⁻²¹

In this study, the association of new symptoms with atopy and changes in methacholine PD_{20} implies an inflammatory or possibly allergic mechanism. The lack of effect of nedocromil, however, suggests that allergen induced asthma is unlikely to be responsible. A reflex mechanism (perhaps similar to the effects of capsaicin) might be responsible, but this would not explain the changes in bronchial reactivity. It is possible that the present study was too short and had too few patients to demonstrate the effect of nedocromil, but the differences between placebo and treated groups were extremely small.

The mechanism underlying symptoms induced by grain dust remains uncertain. This study provides no evidence that grain dust has a byssinosis like effect in that there was no effect of time of week on changes in FEV_1 , and only one subject showed any daytime decline in FEV_1 . The most important influence on changes in FEV_1 was time of day, and this clearly needs to be considered in all future studies of shift related change in FEV_1 in grain workers.

The lack of correlation between exposure to grain dust and symptoms or methacholine PD_{20} suggests that these manifestations of respiratory disease induced by grain dust may not be precisely dose related. This observation, however, may also be the result of the way that symptoms were recorded. Symptoms which occurred after shifts had ended were recorded as being associated with zero exposure to grain, but symptoms developing after work (as commonly occurs in occupational asthma, for example) may be important. Also, the use of self reported dust exposure concentrations may not be as accurate as continuous measures of dust exposure, but continuous recordings were beyond the scope of this study.

We have confirmed other findings in West Australian grain workers—namely, that new symptoms were commoner in atopic subjects and associated with a fall in methacholine PD_{20} . These changes were not accompanied by changes in FEV_1 or FEV_1 over a shift, and the most important influence on shift related change in FEV_1 was time of day. Nedocromil had no effect on the prevalence of symptoms or on the development of new symptoms during the peak of the grain handling season and did not prevent changes in bronchial reactivity.

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