

A double-blind placebo controlled study of a Rye based herbal extract (Oralmat™) in adult asthma; evidence of improvement demonstrated.

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Word Counts.**Abstract: 130 words****Body of text:****ABSTRACT**

OBJECTIVES: To investigate the effects of Oralmat on asthma symptoms and respiratory function in mildly to moderately asthmatic adults.

DESIGN AND SETTING: A double-blinded, randomised investigation of the effects of the commercially available rye-extract, Oralmat™, on asthma symptoms and spirometry measures.

MAJOR OUTCOME MEASURES: Changes in spirometry measures (FEV₁, FEF_{max}, FEF₂₅₋₇₅, FVC), surveyed subjective measures (including wellbeing, asthma symptoms and ability to exercise) and diary records (medication use, sleep disturbance, cough and breathlessness).

RESULTS: We found significant improvements in reported wellbeing, asthma symptoms and ability to exercise. There were no consistent, statistically significant changes in other surveyed subjective measures, spirometry measures or diary entries.

CONCLUSIONS: This study suggests that Oralmat may alleviate discomfort associated with asthma. Further research is needed to confirm the role of Oralmat in asthma treatment.

Keywords: Oralmat™, asthma, herbal medicine, complementary medicine (Check MeSH headings - see Index Medicus)

Introduction

Asthma has profound effects on patients, their families and the community. Poorly controlled asthma can reduce patients' wellbeing, and interfere with their ability to exercise and to participate in sport and community activities. Asthma can even result in loss of employment¹. The 1989 cost of lost production due to asthma in NSW has been estimated to be \$48 million². Hence reducing the impact of asthma is an important health-care goal in both social and economic terms.

Many patients turn to complementary and alternative medicines as they strive to control their asthma. In a 1999 survey, 55% of children with asthma had used at least one alternative therapy³. Although only 4% of patients in that survey and 8% of patients in a 1997 survey⁴ used herbal asthma treatments, 43% of adult asthmatics interviewed in a 1998 survey⁵ thought herbalism was useful to "a great" or "some" extent. That study also found that herbal therapy usage was greater among patients with very severe asthma (15%) than among patients with mild asthma (8%).

The use of dietary supplements, including herbal medicines, may be increasing. In an audit of 600 files from patients with atopy, Mullins⁶ found an increase in the use of dietary supplements from 7.5% in 1995 to 25% in 1997. Echinacea use was nil, 5% and 3% in 1995, 1996 and 1997, respectively.

Herbal remedies should not be dismissed without investigation. Disodium cromoglycate (Intal) was originally extracted as "khellin" from the root of the Egyptian plant *ammivisnaga*⁷.

The ill-considered use of herbal remedies may endanger patients. Herbal preparations may be intrinsically hazardous, or may become hazardous due to misidentification or substitution of plants, poor standardisation, preparation or labelling, adulteration or contamination⁸.

Allergenicity is one intrinsic hazard of dietary supplements and herbal medicines, which should be of particular concern to asthmatic patients and their doctors. This hazard has been demonstrated by asthmatic and anaphylactic reactions to royal jelly⁹ and echinacea⁶.

Lane and Lane⁷ warned that alternative medicines might endanger asthmatic patients by impairing awareness of airway obstruction. This warning may explain the finding⁴ that patients who attempted self-treatment with herbal medicine were at greater risk of hospitalisation for asthma than were other patients. This increased risk may also have been caused by delays in medical treatment, incurred as patients sought relief using alternative remedies.

Given the potential for both benefit and harm from herbal remedies, clinicians need information, obtained from well-designed clinical trials, about herbal asthma remedies. A comprehensive survey¹⁰ found only two randomised trials investigating herbal asthma treatments.

In response to this paucity of evidence, Edvard Ernst called for randomised, clinical trials to enable clinicians to advise their patients about the risks and benefits of herbal treatments¹¹.

We carried out a randomised, four-week study, investigating changes in subjective and objective measures of asthma, among adult asthmatic patients taking Oralmat, a commercially available rye-extract. During this study, patients taking Oralmat reported improved wellbeing, asthma symptoms and ability to exercise. Patients taking the placebo did not report equivalent improvements.

Methods

We used a randomised, placebo-controlled, double-blinded group design to investigate the effects of a commercially available rye-extract, OralmatTM, on subjective and objective measures of asthma.

Patient selection and allocation

Thirty-seven adult patients (19 male, 18 female) with mild, stable asthma were recruited into the study between May and December 1998. Patients were recruited through a newspaper advertisement, radio interviews and “word of mouth”. Mild stable asthma was defined by a previous diagnosis of asthma; at least a 20% fall in FEV₁ in response to a hypertonic saline bronchial challenge⁽¹²⁾, and no history of life-threatening asthma. Patients were excluded if, on testing or history, they were judged to have severe, unstable asthma, any other form of airway disease or other significant illness. Patients were informed of their right to withdraw from the study at any time.

After patients recruited to the study gave their informed consent to participation, each patient was assigned a number and subsequently randomised into either the Treatment (OralmatTM Drops Solution – Manufactured by Schumacher Pharmaceuticals Pty Ltd) or the Placebo group. To protect the privacy of patients and the integrity of the study, the manufacturers were never informed of patient identities. The investigators and patients remained blinded to patient allocation until all measurements and questionnaires had been completed.

Treatment

The manufacturers provided the Oralmat/placebo to the pharmacy at John Hunter Hospital, in vials already labelled with patient numbers. After each patient had completed an initial questionnaire and baseline spirometry, and these had been scrutinised for any reasons for exclusion, he or she was provided with the assigned vial.

Patients were asked to self-administer the Oralmat/placebo by placing three drops under the tongue, three times each day until the final (week 4) measurements were completed.

Measurements

Each patient completed an initial questionnaire, prior to the commencement of treatment, on his or her general medical history, his or her history of asthma, the current severity, treatment and triggers of the asthma, and other potentially relevant medical information. This questionnaire was scrutinised for reasons for exclusion, and was used both for characterisation of the patient sample and for comparisons of the pre-treatment health status of the treatment and placebo groups.

Patients were asked to keep a daily record (diary) of symptoms and medication during the study, and to complete follow-up questionnaires after one and four weeks of treatment. These latter questionnaires investigated the patients' perceptions of symptomatic changes on a scale of -3 (worse) through 0 (same) to 3 (better), as well as any changes in medication use during the trial.

At week 0, week 1 and week 4 of the study, lung function was measured using a Medical Graphics PF/Dx 1085 Spirometry System, according to recommended techniques. Patients were asked not to use bronchodilators less than two hours before spirometry. Following the initial spirometry, 2 ml of salbutamol (2.5mg/ml), combined with 2 ml of normal saline, was administered by nebuliser. Ten minutes subsequently, spirometry was repeated. This spirometry provided measurements of FVC, FEV₁, FEF_{Max} and FEF_{25-75%}, before and after bronchodilator use.

A blood sample was collected from each patient at week 0, week 1 and week 4 of the study. These samples were analysed for relevant haematological and immunological and

biochemical characteristics. Each patient's sitting blood pressure was measured during each visit.

Analyses

Data were analysed using Microsoft Excel '97 and SPSS for Windows.

The medical profile of the patient group was expressed in terms of pre-treatment spirometry and the patients' responses to the initial questionnaire. Pre-treatment differences between the treatment and placebo groups were assessed using Chi-squared analyses of patient responses to the initial questionnaire and Students' t-tests performed on pre-treatment spirometry measurements.

Between-treatments differences in patients' responses to the follow-up questionnaire were assessed using the Mann-Whitney test of two medians.

Changes in week 1 spirometric measures, expressed as percentages of predicted values, were calculated as the difference between the week 1 and week 0 values, expressed as a percentage of the week 0 values. The same calculation was performed for the week 4 spirometric measures. Between treatments, differences in mean scores for these values were assessed using MANOVA and Student's t-test.

Between-treatments differences in mean scores for the haematological, immunological and biochemical measures (expressed as percentages of predicted values, where appropriate) were assessed using Student's t-test.

Diary records were summed separately for each patient and each question, for days 1 to 5 (Sum 1) and for days 24 to 28 (Sum 2). The differences between Sum 1 and Sum 2 were calculated and a Mann-Whitney test was used to compare these differences between the Oralmat and placebo groups.

Some patients ceased taking preventative medications during the experiment. To determine the effects of these changes on the results, the above calculations were repeated with the omission of these patients.

Results

Pre-treatment Characteristics

We found no significant pre-treatment differences between the treatment and placebo groups in any of the measured or surveyed parameters.

In the pre-treatment questionnaire, 60% of patients reported experiencing an asthma exacerbation in the previous year, with 27.8% reporting an exacerbation in the previous month. Eight percent reported a hospital admission due to asthma in the previous year. Slightly over half (52.8%) of the patients said they coughed regularly, while 88.9% reported wheezing in the previous year. Two-thirds of patients reported night or early morning awakening due to asthma.

Pre-treatment mean values for all spirometry measures fell below the population mean (100%), with the lowest mean measure being 66.4%, for pre-bronchodilator FEF_{25-75%}, and the highest mean measure being 97.2%, for post-bronchodilator FVC (Table 3).

3: Mean spirometry measures (all patients) prior to treatment								
MEASUREMENT	FEV ₁	FEV ₁	FVC	FVC	FEF _{MAX}	FEF _{MAX}	FEF _{25-75%}	FEF _{25-75%}
PRE/POST BRONCHODIL.	PRE	POST	PRE	POST	PRE	POST	PRE	POST
MEAN	87.1	91.2	95.7	97.2	96.9	92.8	66.4	76.9
STANDARD DEVIATION	24.4	23.8	19.4	18.4	25.9	23.1	35.3	38.5

Questionnaires

Patients taking Oralmat reported significantly greater improvements in wellbeing ($p < 0.01$) and asthma symptoms ($p < 0.01$) during week 1 of the study, and in wellbeing ($p < 0.01$) and ability to exercise ($p < 0.05$) during week 4 of the study, than did patients taking the placebo (Figures 1 to 6; Table 4).

After omission of the responses of patients who had changed their medication regimen, patients taking Oralmat reported significantly greater improvements in wellbeing ($p < 0.01$), asthma symptoms ($p < 0.01$) and ability to exercise ($p < 0.05$) during week 1 of the study, and in wellbeing ($p < 0.05$) and ability to exercise ($p < 0.01$) during week 4 of the study, than did patients taking the placebo.

We found no significant differences in other questionnaire responses between patients taking Oralmat and those taking the placebo.

4: Responses to follow-up surveys on patients' perceptions of health changes

	WEEK 1					
	ORALMAT			PLACEBO		
	better	same	worse	better	same	worse
General wellbeing	10	7	1	2	14	2
Asthma symptoms	10	6	2	0	13	5
Ability to exercise	8	8	2	4	13	1

	WEEK 4					
	ORALMAT			PLACEBO		
	better	same	worse	better	same	worse
General wellbeing	10	4	1	5	8	3
Asthma symptoms	9	6	0	6	9	1
Ability to exercise	10	5	0	4	10	2

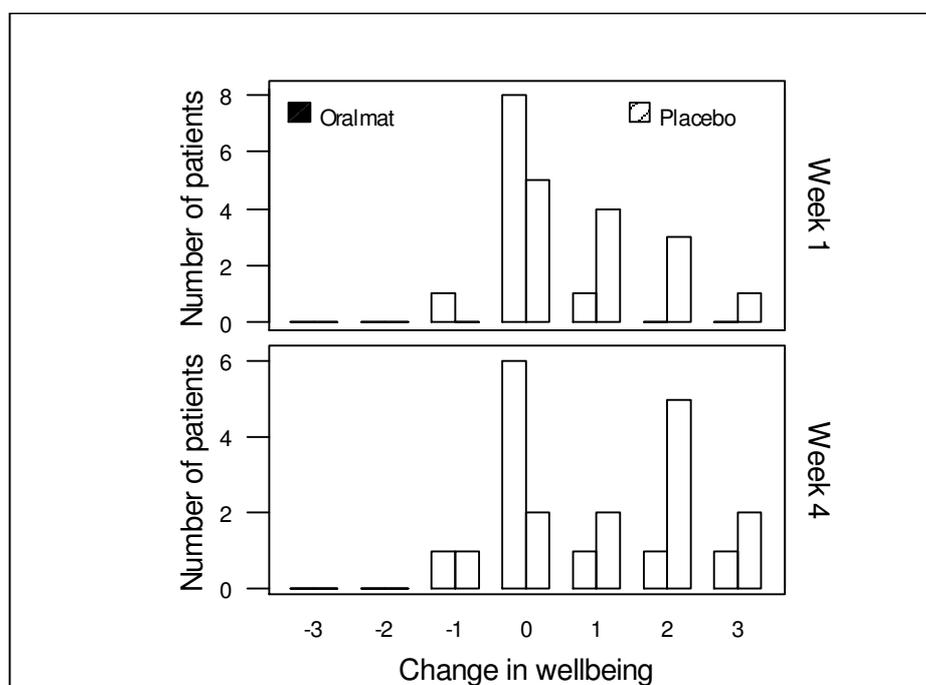


Figure 1: Perceived changes in wellbeing among patients taking Oralmat or a placebo (Patients who continued taking preventative medicine)

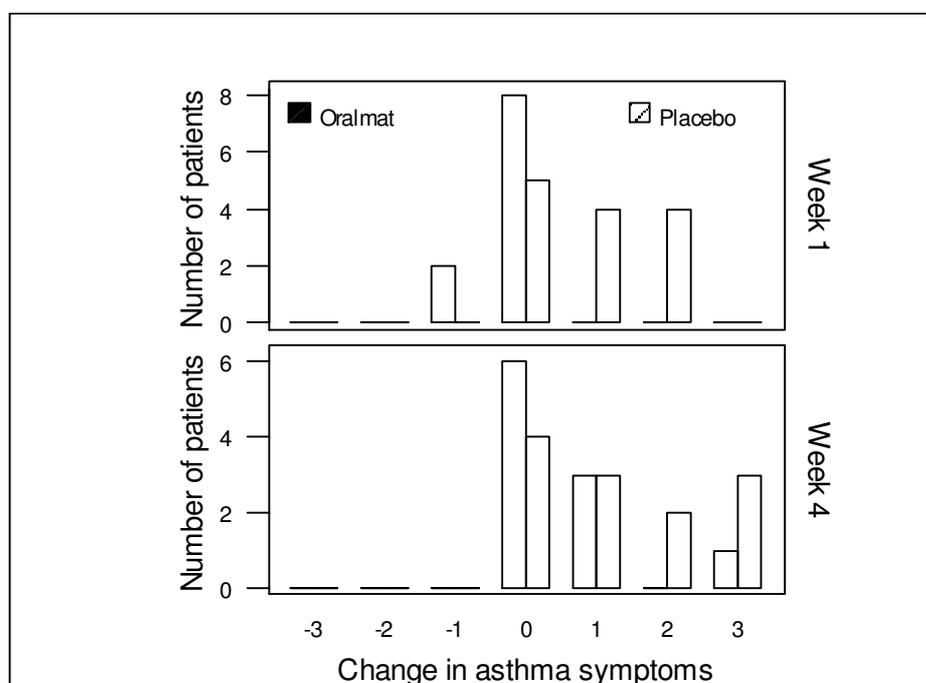


Figure 2: Perceived changes in asthma symptoms among patients taking Oralmat or a placebo (Patients who continued taking preventative medicine)

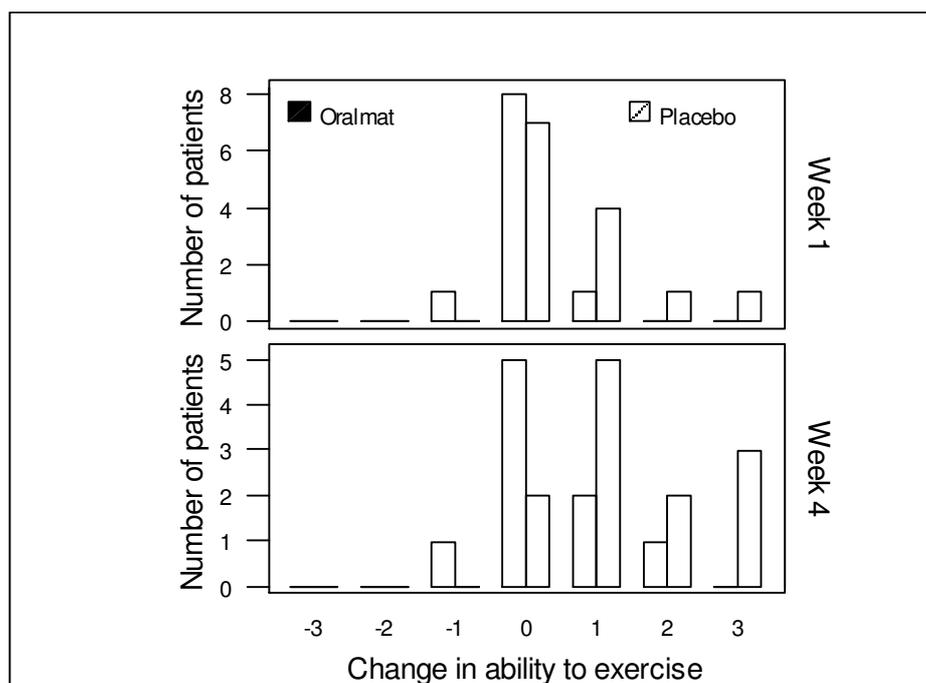


Figure 3: Perceived changes in ability to exercise among patients taking Oralmat or a placebo (Patients who continued taking preventative medicine)

We found no significant differences between the Oralmat and placebo groups in blood pressure, in haematological, biochemical or immunological measures, or in symptomatic changes reported in patient diaries.

Discussion.

Patients taking Oralmat reported greater improvements in wellbeing, asthma symptoms and ability to exercise than did patients taking the placebo. These differences were statistically significant, and continued to be significant once patients who had ceased taking preventative medications were omitted from the analyses.

Why were significant differences between the Oralmat and placebo groups found for these variables, but not for other surveyed variables or for variables reported in the patient diaries? Although all patients reported some asthma symptoms, and these symptoms were likely to affect both patients' wellbeing and ability to exercise, the nature of patients' symptoms varied. Only 19 patients reported coughing more than once a week, and eight patients reported regularly coughing up sputum. Similarly, in the patient diaries, only 11 patients reported any sleep disturbance during the first 5 days of the study. Also in this diary, twenty-two patients reported coughing and 20 patients reported breathlessness during the first 5 days of the study. The smaller number of patients reporting these specific symptoms reduced the chance that we would find any statistically significant improvements in these symptoms.

In view of the absence of objectively measured changes, such as changes in spirometric measures, how much weight should we give to changes in subjective measures? Subjective measures of asthma can be deceptive, as patients may underestimate their level of airway obstruction¹³. However, spirometric measures do not always reflect disease processes such as hyperinflation and airways plugging¹³. The reversal of hyperinflation, as asthma treatment reduces bronchial inflammation, may vitiate improvements in forced expiratory volume¹⁵. Conversely, significant symptomatic improvements may be noted during treatment, as decreasing residual volume improves lung compliance¹⁵.

In consequence, patients may report changes in asthma symptoms without parallel changes in spirometry measures. In a study by Juniper *et al.*¹⁶, patients reported improvements in their asthma and reduced bronchodilator use during twelve months of treatment with budesonide, despite the absence of any improvement in FEV₁. Patients taking the placebo did not report any significant improvement in symptoms or in bronchodilator use. A pioneering study of Intal¹⁷ found significant, even "striking", symptomatic improvements, but noted that "reliance

on simple spirometry alone would have led to a failure to recognise the therapeutic value of FPL670 [Intal] in six of the ten patients.”

Considered alone, reported improvements in subjective measures would be insignificant but, in the context of a randomised double-blinded clinical trial, they cannot be dismissed. If the improvements in subjective measures reported by patients taking Oralmat occurred in response to other factors (increased contact with medical and nursing staff, for example) we would expect patients taking the placebo to report equivalent improvements. Although there was a slight trend to improvement in the placebo group during week 4, this was significantly less than that in the Oralmat group. There was no trend toward improvement in the placebo group during week 1.

What caused the reported improvements in asthma symptoms among patients taking Oralmat? We found no improvements in lung function, as measured by spirometry. However, limitations in the size of this study meant that only very large differences in spirometric values would have been detected. We cannot conclude, from these results, that Oralmat does not cause objectively measurable changes in lung function.

Reported improvements in asthma symptoms and ability to exercise are not necessarily due to improved lung function. An increased ability to exercise was reported after acupuncture¹⁸. This change was explained as a consequence of a decreased perception of breathlessness in patients whose lung function remained unaltered. Diazepam¹⁹ and dihydrocodeine²⁰ have also been shown to reduce perceptions of breathlessness. Like these treatments, Oralmat may alter perceptions, so that patients are less distressed by their asthma. Such effects should not be disregarded. Treatments that reduce distress due to asthma may be clinically useful. However, care should be taken to ensure that these treatments do not abolish awareness of severe airway obstruction⁷.

Further studies are needed to verify the effects of Oralmat. Ideally, these studies should use a crossover design, involving sufficient patients to facilitate identification of clinically significant spirometric effects.

If further clinical trials support the finding that Oralmat has a beneficial effect on asthma symptoms, researchers will need to investigate potential sources of improvement. Analyses of

Oralmat should be performed, concurrently with these clinical trials, to identify ingredients of the extract, and to determine which ingredients are present in potentially bioeffective quantities.

In view of this report, clinicians may choose to give qualified support to the use of Oralmat by patients who are seeking complementary asthma treatment. It is important to stress to patients that this remedy should not replace conventional treatments, but should only be used as a supplement, at least until further evidence is available.

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