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Effects of dimethindene maleate nasal spray on the quality of life in seasonal allergic rhinitis*

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SUMMARY

***Objective**: To determine if the H_1-receptor antagonist dimethindene maleate (DMM), topically applied, is able to improve the quality of life (QoL) in patients with seasonal allergic rhinitis better than placebo.*

***Methods**: The study was a multi-centre, randomised, placebo-controlled, double-blinded phase III trial including 157 patients. Two parallel groups received either DMM nasal spray or placebo for 2 weeks. Patients answered 5 QoL questionnaires (Rhinoconjunctivitis QoL Questionnaire {LQ-AR}, Munich Life Dimension List {MLDL}, Profile of Mood States {POMS}, 2 Visual Analogue Scales {VAS-QoL, VAS-GES}) on days 1, 4, 8, and 15.*

***Results**: QoL improved significantly in all scales and groups. Statistically significant differences between groups were achieved in the sub-scales LQ-AR Eye Symptoms and Daily Activities, MLDL Total, POMS Depression and Energy, VAS-QoL and VAS-General Health. All differences favoured the DMM group and were present initially but disappeared in visit 4, except MLDL Total and POMS Energy. Almost all other scores had a better tendency of DMM.*

***Conclusion:** A significant improvement of QoL was found in both groups. Only weak differences between groups (in favour of DMM) were found. There are several reasons explaining this outcome, mainly the rainy weather during the study period (mean weather index 10-20% less sunny than in previous seasons).*

Key words: allergic rhinitis, antihistamine, dimethindene, quality of life

INTRODUCTION

The evaluation of the QoL in patients suffering from chronic diseases is becoming more and more routine in clinical pharmacological studies as well as in clinical practice. The concept of quality of life has been defined as the evaluation of four domains of individual life: physical condition, psychological well-being, social integration, and functional capacity (Bullinger, 1991; Lund, 2001). The individual perception of the grade of impairment of quality of life differs from patient to patient and is influenced by factors like age, gender, religion and education (Lütterfels, 1991). Health-related quality of life refers to the impairment of quality of life by the symptoms of a disease and its therapy (Schipper et al., 1990). Clinical investigations revealed that the objectively measured intensity of symptoms of allergic rhinitis such as nasal obstruction, itching, sneezing and rhinorrhea shows only weak to moderate correlation with the by the patient perceived rhinoconjunctivitis-specific quality of life (De Graaf-in´t Veld et al.,1996; Juniper et al., 1991). Bousquet et al. (1994) demonstrated that patients suffering from allergic rhinitis tend to estimate their quality of life as worse than patients with asthma.

Due to the fact that allergic rhinitis with 10-20% prevalence and increasing tendency is the most common immune disease of the population in western countries (Filiaci et al., 1983; Sibbald et al., 1990; Mygind et al., 1996) and is accompanied by a significant impairment of quality of life (Juniper et al., 1991; Bousquet et al., 1994; Juniper, 1997), it appears obvious for the treatment of allergic rhinitis to aim for an improvement of the quality of life. H1-receptor antagonists have been shown to improve the quality of life in patients with allergic rhinitis (Bellioni et al., 1996; Pariente et al., 1997; Meltzer et al., 1999). Topical antihistamines like azelastine and levocabastine allow

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local application with reduction of common side effects such as drowsiness and headaches (Swedish GP Allergy Team, 1994; Bachert et al., 1996; Davies et al., 1996). Dimethindene (dimethindene maleate (DMM), CAS 3614-69-5, Fenistil resp. Foristal) is a very potent and well established antihistamine that is available as a nasal spray. Because (DMM) is expressing a strong affinity to the H_1-receptor antagonist it is a promising drug to improve the quality of life in patients with seasonal allergic rhinitis upon topical application (Lau et al., 1990). It was tested earlier following topical nasal application in patients suffering from pollen-associated rhinitis, and demonstrated that it exerts the typical antihistaminic effects on general nasal and also, ocular symptoms in a clinically relevant extent (Kyrein et al., 1996; Horak et al., 2000). This clinical trial was designed to test a disease-specific quality of life questionnaire and to investigate if the quality of life in patients suffering from seasonal allergic rhinitis can be improved by a 0.1% DMM nasal spray.

MATERIALS AND METHODS

Study design

The presented study was a prospective, multi-centre, randomised, placebo-controlled, double-blinded phase III clinical trial with 2 parallel-groups. Included were data from 157 patients between 18 and 69 years of age suffering from seasonal allergic rhinitis for at least one season confirmed by either a prick skin test or RAST. Seventy-six patients were in the verum-group, 81 patients in the placebo-group. Ninety-five% (92%) of the patients in the verum-group (placebo-group) had moderate to severe symptoms on inclusion based on history, physical examination and rhinoscopy. The time period for inclusion was the summer season of 1996. The groups received 0.28 ml nasal spray twice daily containing either 0.1% DMM solution or placebo for two weeks. Each puff contained 0.14 mg DMM in 0.14 ml solution or placebo. The patients were instructed to provide one puff in each nostril twice daily. Thus the total dosage was 0.56 mg DMM in 0.56 ml solution per day or the same amount of placebo. The placebo was a NaCl-based solution containing benzalconium chloride. The compliance was determined by weighing the returned bottles and was found to be adequate. Patients also received xylometazoline nasal spray and cromolyn sodium eye drops on visit 2 (day 4±1) which was allowed to be used as needed.

Exclusion criteria included any overlapping disease of the nose and throat, asthma, pregnancy, hypersensitivity, psychiatric diseases and drug abuse. Previous medication with a defined list of substances that interfere with the action of H_1-receptor antagonists was prohibited 4 weeks before and during inclusion.

The quality of life was assessed four times during 2 weeks on the treatment days (Visits) 1, 4(±1), 8(±2) and 15(±2). A weather index was introduced in order to take unsteady weather into account. Four different grades of weather conditions were defined from sunny to rainy.

QoL instruments

Rhinoconjuntivitis Quality of Life Questionnaire (LQ-AR)

This questionnaire has been developed by Juniper et al. (1991). It evaluates domains of QoL that are directly linked to the symptoms of allergic rhinitis. The German version has already been validated (Zander et al., 1993a; Zander et al., 1993b). The questionnaire contains 28 questions about sleep disturbance (3 questions), tiredness and headache (7 questions), practical problems (3 questions), nasal symptoms (4 questions), eye symptoms (4 questions), impairment of daily activities (3 questions) and emotional state (4 questions). Each question has to be answered on a 7 point scale. The quality of life is expressed as the mean of these 7 domains. Recently, Juniper et al. (1999) published the standardised and validated version of this questionnaire.

Munich Life Dimension List (MLDL)

This questionnaire has been developed by Heinisch et al. (1991). It contains 19 questions regarding four domains of quality of life on an 11 grade scale: physical condition, psychological well-being, social integration and functional capacity. Grade 0 means “I was unsatisfied with ...”, grade 10 means “ I was very satisfied with ...”.

Profile of Mood States (POMS)

This questionnaire evaluates the mental well-being and was developed by McNair et al. (1971). It lists 35 adjectives describing states of emotions. The patient has to mark on a scale measuring from 1 (“not at all”) to 4 (“very much”), how much the emotional state described corresponds to his or her personal mood.

Visual-Analogue-Scale for Quality of Life (VAS-QoL)

The VAS-QoL is a horizontal line of 10 cm in length on which the patient marks his overall quality of life during the past few days. The left pole marks “My quality of life could not have been worse”, the right pole marks “My quality of life could not have been better”. The quality of life is measured by the distance between the left pole and the patient’s mark. The VAS has been originally developed by Huskisson (1974) for the measurement of pain levels.

Visual-Analogue-Scale for Appraisal of General Health (VAS-GES)

This VAS is analogue to the VAS-QoL. The left pole means “My general health could not have been worse”, the right pole means “My general health could not have been better”.

Study protocol

This multi-centre trial was conducted in 20 centres of the German Rhinitis Study Group, consisting of physicians of Otorhinolaryngology and Primary Care Medicine. Patients were selected by the physicians and included if found eligible. A written consent had to be provided. Inclusion followed after

Table 1. Distribution of patients on inclusion in percent of the population per group.

	DMM	Placebo
Gender: Female	55.3%	58%
Male	44.7%	42%
Moderate to severe symptoms	95%	92%
Moderate to severe impairment at work	69%	79%
Moderate to severe impairment during leisure time activities	78%	88%
Moderate to severe impairment in social activities	72%	69%
Moderate to severe impairment conducting sports	72%	69%

the patient matched all criteria. A complete history and physical examination for health screening followed. On the first visit a questionnaire on the life circumstances was completed which served to demonstrate homogenity of the population. It contained questions on gender, age, educational and employment status, social life and severity of the rhinoconjunctivitis symptoms. On each of the 4 visits during the time period of 2 weeks patients completed the LQ-AR, MLDL, POMS, VAS-QoL and VAS-GES. Using a block-randomisation system identical bottles containing either dimethindene maleate or placebo nasal spray were handed out to the patients with instructions to administer one puff into each nostril in the morning and the evening. Patients returned on day 4(±1), 8(±2) and 15(±2). On visit 2 (day 4±1) a second bottle was handed out together with the emergency medication xylometazoline nasal spray and cromolyne sodium eye drops.

Statistical analysis

The variables for statistical analysis were derived from the scales of the questionnaires LQ-AR, MLDL, POMS, VAS-Qol and VAS-GES. Statistical tests were conducted on a significance level of 1%, 5% and 10% in a 2-tailed as well as 1-tailed fashion. We compared the distribution within each group and each visit. Also groups were compared before and after adjustment to the baseline-values of visit 1. ANOVA tests were conducted using the General-Linear-Model procedure of the SAS software. For the detection of small differences the Wilk's λ test was used. The treatment was the independent variable, visits 1 to 4 were the dependent variables.

Before analysis some scales were converted so that a higher score reflected a better quality of life. The mean of each parameter was determined and tested with the t-test for the dependent matrix. The Friedman test was used for the descriptive p-value for homogenous distribution of more than 2 dependent groups. The Mann-Whintney U-test (Wilcoxon rang-sum test) was used to compare 2 independent groups. Comparisons were conducted on a 1%, 5% as well as 10% significance level.

RESULTS

The distribution between the groups was homogenous regarding gender, age, education, employment, severity of symptoms, impairment of social and leisure activities and sports (Table 1).

Rhinoconjunctivitis Quality of Life (LQ-AR)

The scales showed a reduction of the scores representing an improvement of the quality of life in both groups and in all 4 visits ($p \leq 0.001$). Only the sub-scales LQ-AR Eye Symptoms ($p \leq 0.10$) and LQ-AR Daily Activities ($p \leq 0.10$) showed statistically significant differences between the DMM and the placebo group only in visit 3 when the scores were adjusted to the baseline from visit 1. The Eye Symptoms score reduced in the DMM group by 56% ($p \leq 0.10$) on visit 3 compared to visit 1 and by 42% ($p \leq 0.10$) in the placebo group. In Daily Activities the DMM score reduced by 56% ($p \leq 0.10$) in visit 3 compared to visit 1 and the placebo score reduced by 38% ($p \leq 0.10$). Nevertheless, the sub-scales Practical Problems and Emotions also exhibited a better trend in the DMM group whereas Sleep, Non-hayfever Symptoms and Nasal Symptoms had better scores in the placebo group (Table 1, Figures 1 and 2).

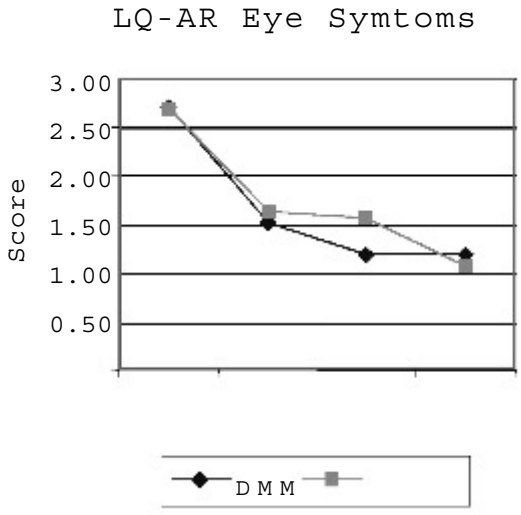

Figure 1. LQ-AR Eye Symptoms. Score with statistically significant difference between groups in visit 3 ($p \leq 0.10$). The lower score in the DMM group represents a stronger reduction of eye symptoms compared to placebo.

Munich Life Dimension List (MLDL)

The MLDL showed a significant increase of scores over time in all sub-scales and in both groups ($p \leq 0.001$). A higher score represents a better quality of life. Upon adjustment to the baseline on visit 1, only the MLDL Total sub-scale showed

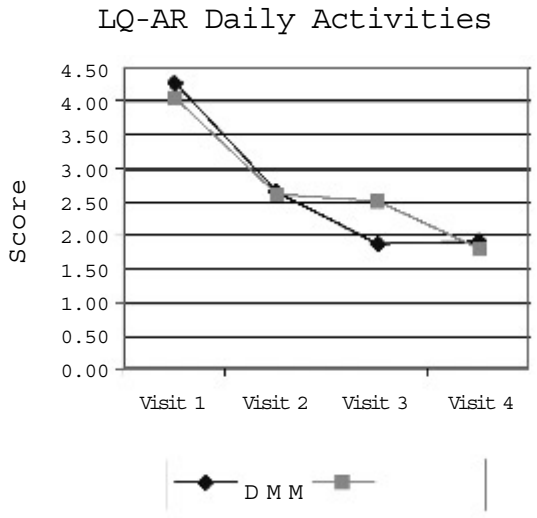

Figure 2. LQ-AR Daily Activities. Score with statistically significant difference between groups in visit 3 (p≤0.10). The lower score in the DMM group represents more reduced impairment of the ability to conduct daily activities compared to placebo.

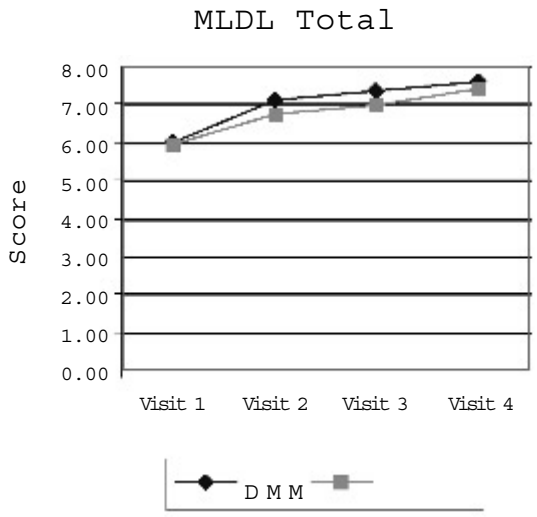

Figure 3. MLDL Total. Score with statistically significant differences in visit 2 (p≤0.10) and visit 3 (p≤0.05). The higher score in the DMM group represents an overall higher increase of quality of life regarding the domains of the MLDL questionnaire compared to placebo.

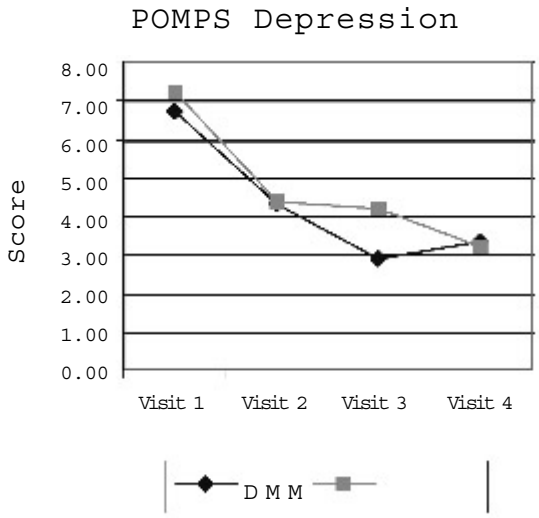

Figure 4. POMS Depression. Score with statistically significant difference in visit 3 (p≤0.05). The lower score in the DMM group represents more reduced depression compared to placebo.

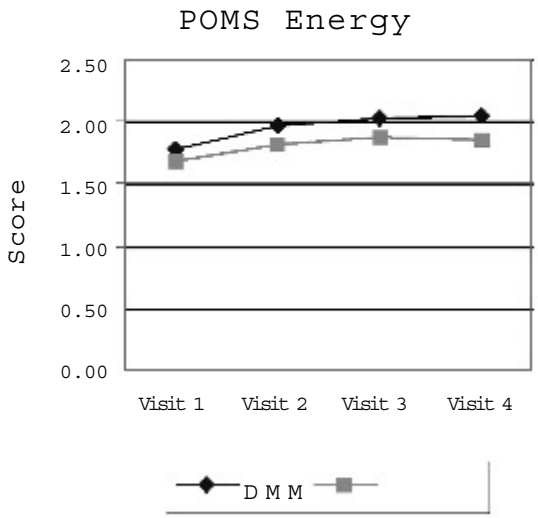

Figure 5. POMS Energy. Score with statistically significant difference in visit 4 (p≤0.10). The higher score in the DMM group represents a higher increase of energy compared to placebo.

significant differences between the two groups on visit 2 with a 19% (13%) score increase in the DMM (placebo) group (p≤0.10), and in visit 4 with a 27% (25%) score increase in the DMM (placebo) group (p≤0.05) compared to visit 1. All other sub-scales did not show statistically significant differences. However, the trend in all scales was a better score in the DMM group (Table 1, Figure 3).

Profile of Mood States (POMS)

In the POMS scales there was continuous improvement of quality of life over time (p≤0.001). In POMS Energy on visit 4 there was a 15% score increase in the DMM group compared to visit 1 whereas the placebo score increased only by 11% (p≤0.10). When adjusted to the baseline, the scale POMS Depression also showed significant difference between the groups on visit 3. The DMM score reduced by 57%, the placebo score by 42% compared to visit 1 (p≤0.05). All other scores did not achieve statistical significance (Table 1, Figures 4 and 5).

Visual Analogue Scale Quality of Life / General Health (VAS-QoL / VAS-GES)

The VAS-QoL as well as VAS-GES exhibited increase of scores over time in both groups (p≤0.001). Only on visit 2 there was a significant difference between the groups in both scales. In the VAS-QoL scale there was a 25% score increase in the DMM group compared to visit 1 and a 15% score increase in the placebo group (p≤0.05). In the VAS-GES scale there was a

Table 2. Mean scores in each scale on visit 1 to 4 for each group. Scores with statistically significant differences between groups are framed. LQ-AR Eye Symptoms and Daily Acitivities in visit 3 (p≤0.10); MLDL Total in visit 2 (p≤0.10) and visit 4 (p≤0.05); POMS Depression in visit 3 (p≤0.05) and Energy in visit 4 (0.10); VAS-Qol and VAS-GES in visit 2 (p≤0.05).

Scales	Visit 1		Visit 2		Visit 3		Visit 4	
	DMM	Placebo	DMM	Placebo	DMM	Placebo	DMM	Placebo
LQ-AR								
Sleep	2.74	3.20	1.71	1.90	1.38	1.65	1.20	1.29
Non-Hayfever Symptoms	2.91	3.18	1.94	2.14	1.60	1.88	1.50	1.62
Practical Problems	4.33	3.98	2.78	2.61	2.40	2.29	2.06	2.02
Nasal Symptoms	3.82	3.89	2.43	2.66	2.03	2.25	1.88	1.77
Eye Symptoms	2.69	2.67	1.51	1.63	1.18	1.56	1.19	1.07
Daily Activities	4.24	4.04	2.64	2.59	1.85	2.51	1.89	1.81
Emotions	2.52	2.34	1.41	1.52	1.02	1.32	0.93	0.94
Total	3.18	3.23	1.99	2.11	1.62	1.87	1.48	1.48
MLDL								
Physical Condition	5.18	5.02	6.70	6.20	6.94	6.60	7.22	6.97
Psychological Well-Being	5.32	5.08	6.78	6.35	7.10	6.74	7.26	7.18
Social Integration	7.12	6.87	7.72	7.25	7.67	7.45	7.95	7.78
Functional Capacity	6.56	6.63	7.27	7.06	7.52	7.19	7.71	7.43
Total	5.97	5.91	7.08	6.70	7.30	6.99	7.56	7.37
POMS								
Depression	0.67	0.72	0.43	0.44	0.29	0.42	0.33	0.32
Tiredness	1.74	1.74	1.15	1.28	0.96	1.13	0.91	0.89
Energy	1.78	1.67	1.96	1.81	2.02	1.87	2.04	1.85
Irritability	1.04	1.08	0.73	0.79	0.56	0.73	0.56	0.55
VAS-QoL	49.52	47.54	62.09	54.86	63.63	60.84	65.99	62.49
VAS-GES	44.42	40.62	59.66	52.70	61.10	57.94	62.46	60.87

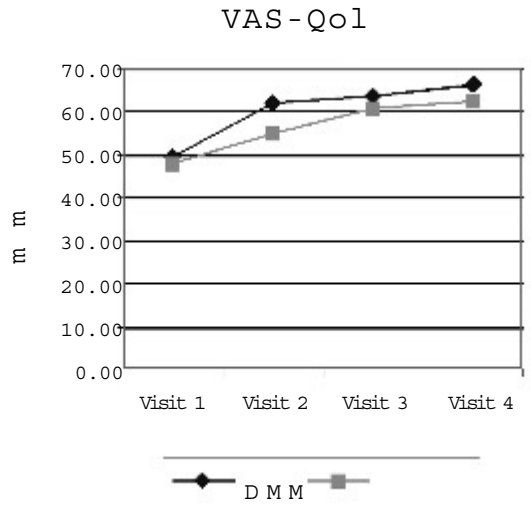

Figure 6. VAS-QoL. Score with statistically significant difference between groups in visit 2 (p≤0.05). The higher score in the DMM group means an overall more pronounced improvement of the quality of life compared to placebo.

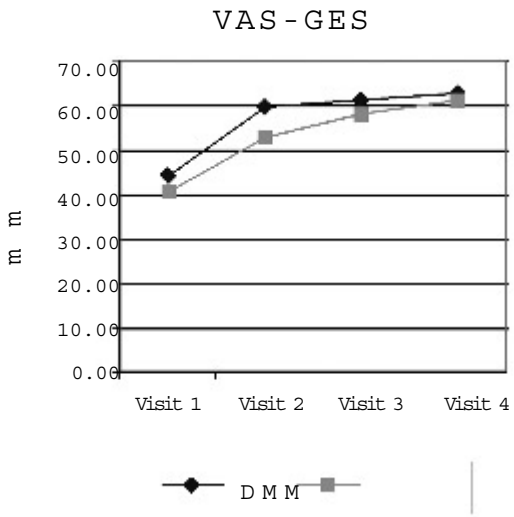

Figure 7. Visual Analogue Scale for General Health. Score with statistically significant difference in visit 2 (p≤0.05). The higher score in the DMM group represents a more pronounced improvement in general health compared to placebo.

34% score increase in the DMM group in visit 2 compared to visit 1 and a 30% score increase in the placebo group ($p \leq 0.05$). However, when the scores were adjusted to the baseline only the VAS-QoL showed statistical significance in visit 2 ($p \leq 0.10$). The scores were higher in the DMM group, representing a better quality of life and general health (Table 1, Figures 6 and 7).

DISCUSSION

The purpose of this study was to determine the effects of dimethindene maleate nasal spray on the quality of life of patients suffering from seasonal allergic rhinitis compared to placebo. Allergic rhinitis with its increasing prevalence (Sibbald et al., 1990) was shown to have a significantly high impact on the quality of life leading to decreased performance at work and learning impairment in children (Vuurman et al., 1993; Simons, 1996). Therefore, anti-allergic treatment should aim for the improvement of quality of life in these patients.

The groups revealed to be homogenous in terms of demographic parameters such as age, gender, educational level, number of children and friendships. Also parameters such as impairment at work and during leisure time as well as the weather score on visit 1 were homogenous in the DMM and the placebo group.

In all questionnaires there was a significant improvement of quality of life over time in both groups but at first there were no statistically significant differences between the groups. Only after more sensitive testing and adjustment to the baseline of visit 1, few sub-scales expressed significant differences between the groups, all of which were in favour of the DMM group. A stochastic distribution of randomly significant differences would show results in both direction, emphasising a better efficacy of DMM compared to placebo. It is remarkable that most differences were found on visit 2 or 3 but disappeared on visit 4. Only MLDL Total and POMS Energy have differences on visit 4. We can not determine if these would remain significantly different after a longer period of time.

These results speak for a faster onset of action of DMM compared to placebo but on the last visit scores adjusted. However, there are several reasons that could explain the unimpressive results found in this study. One would have expected to find more significant differences between dimethindene maleate and the placebo since H_1-receptor antagonists have been proven to increase the quality of life in allergic rhinitis patients (Swedish GP Allergy Team, 1994; Davies et al., 1996) and since dimethindene maleate is a highly effective antihistamine (Kyrein et al., 1996). Clinical effectiveness in reduction of nasal symptoms in mild to moderate seasonal allergic rhinitis was demonstrated in an active (azelastine) and placebo-controlled pharmacodynamic dose-finding (Kyrein et al., 1996), an active (disodium cromoglycate, DSCG) and placebo-controlled study (Horak et al., 2000), and a recent placebo-controlled study (Horak et al., 1995), all under standardised conditions with patients being challenged with purified grass pollen in the Vienna Challenge Chamber, an established allergen provocation model in challenge studies. In-vitro investigation showed that azelastine significantly reduces ciliary activity with complete cessation of all ciliary movement while dimethindene resulted in a mild reduction (Alberty et al., 1998). Furthermore effectiveness in symptom reduction under every days life conditions was demonstrated in a clinical study in children with levocabastine as active control. One reason could be that the placebo contains active components. NaCl-based substances have symptom relieving effects on the nasal mucosa with reduced nasal obstruction, itching and postnasal drip (Georgitis et al., 1994). This is probably due to pH-neutralisation of the nasal mucosa and dilution of the allergens.

Another reason for the results in this study was the unusually rainy weather during the study period in the summer of 1996. We established a weather index which revealed a 10 to 20% lower score than in previous seasons indicating unusually rainy weather. Due to the fact that the weather is correlated with the pollen concentration and with the severity of allergy symptoms this could be the most obvious reason for the little effect of DMM on the quality of life in this study.

Furthermore, in this study the questionnaires were designed to ask the patients about the past few days. If the intervals between visits would be smaller it could possibly increase the sensitivity of the questionnaires because this would take unsteady weather into account.

We did not calculate the minimal important difference nor the number needed to treat parameters, which have been more recently introduced by Juniper (1998). Due to this fact we do not know if the few statistical significant differences between DMM and placebo are clinically relevant. All statistically significant differences point to the ability of dimethindene maleate to improve the quality of life and almost all other scores have a better tendency of DMM even though they are not significant.

From today's point of view other treatment options have to be reviewed, particularly as antihistamines give only limited relief to nasal obstruction. Several studies showed recently that topical corticosteroids are able to improve the quality of life in allergic rhinitis more effectively and are less expensive than topical antihistamines (Davies et al., 1993; Juniper et al., 1997; Ratner et al., 1998; Stempel et al., 1998; Stern et al., 1998; Weiner et al., 1998; Ortolani et al., 1999). Topical Azelastine showed no difference to placebo but budesonide showed superior efficacy and tolerability (Stern et al., 1998). Even oral loratadine was less effective on the quality of life than topical fluticasone (Ratner et al., 1998). In a study comparing topical fluticasone versus topical levocabastine, the corticosteroid revealed better control of nasal obstruction and rhinorrhea and was felt to possess overall better clinical effects (Ortolani et al., 1999). Stempel et al. (1998) have screened 13 studies that compare corticosteroids and antihistamines on efficacy, tolerability, effects on quality of life and cost factors and concluded that corticosteroids are more effective and less expensive. The con-

sent today is that topical antihistamines are a treatment option for patients with mild symptoms (Weiner et al., 1998; Van Cauwenberge et al., 2000). Topical antihistamines have a rapid onset of action (less than 15 minutes), while corticosteroids have a relatively slow onset of action and a maximum efficacy only after days and weeks. Thus, topical antihistamines are recommended as "on demand treatment" (Van Cauwenberge et al., 2000). Our results support this consent even though with more sunny weather and higher pollen concentration our study likely would have revealed more impressive results for the efficacy of dimethindene maleate.

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