

Sedation in allergic rhinitis is caused by the condition and not by antihistamine treatment

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Sedation is regarded as a common side-effect of most H_1 -antihistamines. This view must be accepted, yet can hardly be assessed under treatment of allergic disorders. Since central sedative potency is hard to evaluate, different methods of measurement have been introduced in the four phases of clinical investigation. While tests of high complexity in early trials can detect true central effects, they seem to have the disadvantage of not taking into consideration the important interactions of drugs with the disorder. Therefore, we used a visual analog scale (VAS) as an instrument to demonstrate sedative effects in five clinical studies carried out between 1989 and 1994 with a total number of 1070 patients. Thereby, we could assess the result of the different components of the central interaction. In 1989, in a double-blind, placebo-controlled trial, we could show that the vigilance of patients suffering from seasonal allergic rhinitis increased significantly more under treatment with an antihistamine (mizolastine) than under placebo. From 1992 until 1994, we compared azelastine nasal spray either by the double-dummy technique with oral antihistamines (cetirizine, loratadine, and astemizole) or by the double-dummy or placebo-controlled design with monotherapy or combined therapy with azelastine tablets. A marked or statistically significant improvement of vigilance was found for all compounds (loratadine: $P < 0.0001$; cetirizine: $P < 0.0254$; and azelastine nasal spray: $P < 0.1409$ to $P < 0.0001$). Even when taking azelastine as oral application, patients, in spite of the warning, reported a similar increase in vigilance ($P < 0.2628$ to $P < 0.0001$). Finally, we assessed the range of physiologic vigilance using the same VAS in healthy volunteers. In conclusion, we could prove that in all trials the baseline values of vigilance of untreated symptomatic patients were far below physiologic condition and improved under treatment to the upper range of healthy persons. Therefore, any sedative properties of modern H_1 -antihistamines should not limit their therapeutic use, since the truly threatening sedation results from the disorder itself.

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The occurrence of sedation during antihistamine treatment is a well-known fact that can be seen in individual cases (1). Since the sedative potential of some earlier antihistamines occasionally outweighed their therapeutic effect, these compounds are now assigned to the group of sedatives (e.g., promethazine, Atosil[®]). The prerequisite for a central effect resulting from medication is a drug's ability to permeate the blood–brain barrier. This

applies to molecules with a molecular weight < 90 Da and lipophilic character – properties which are not exhibited by some of the new-generation antihistamines. Since sedation is generally assumed to be, among other things, an effect of interaction at central H_3 -receptors, other mechanisms must be present as well (2).

Modern antihistamines are highly effective and nonsedating (3). Nevertheless, adverse experiences

have been reported by individual allergy patients during treatment with these antihistamines (4). The extent of the reported complaints is considerable in some cases; e.g., “falling asleep at the steering wheel in front of a red traffic light” and “falling asleep in court as the presiding judge” (reports from patient diaries in our studies during treatment with nonsedating antihistamines).

If a sedative effect is observed during treatment, qualitative and quantitative classification of its extent is necessary. Psychometric testing methods are preferably employed, allowing a sensitive rating of central stimulation or depression. The selection of the respective methods depends on the number of patients to be examined and the related expenditure. In clinical studies during phase I, a high methodological complexity is accepted, as in the performance of the driving-fitness test (5) and the measurement of motor activity and reflexes as well as electroencephalogram derivations (6).

In the subsequent study phases II–IV, these proceedings are too extensive to be performed with a large patient population. In this case, the central effects are assessed by means of scores, scales, and patient polls. In this context, the visual analog scale (VAS) or KUSTA must be mentioned (7). The drawback of these methods is that unspecific interferences might be rated by the patients as sedation. On the other hand, the application of these methods is advantageous for symptomatic patients, whereas the phase-I studies cannot detect possible and expected interactions between central side-effects and underlying effects of the disorder.

In view of the large number of clinical studies conducted with various antihistamines which have been tested in the past and which were compared against each other and against placebos, a complete overview of the sedative potential of various antihistamines is possible (8). Hence, in a meta-analysis

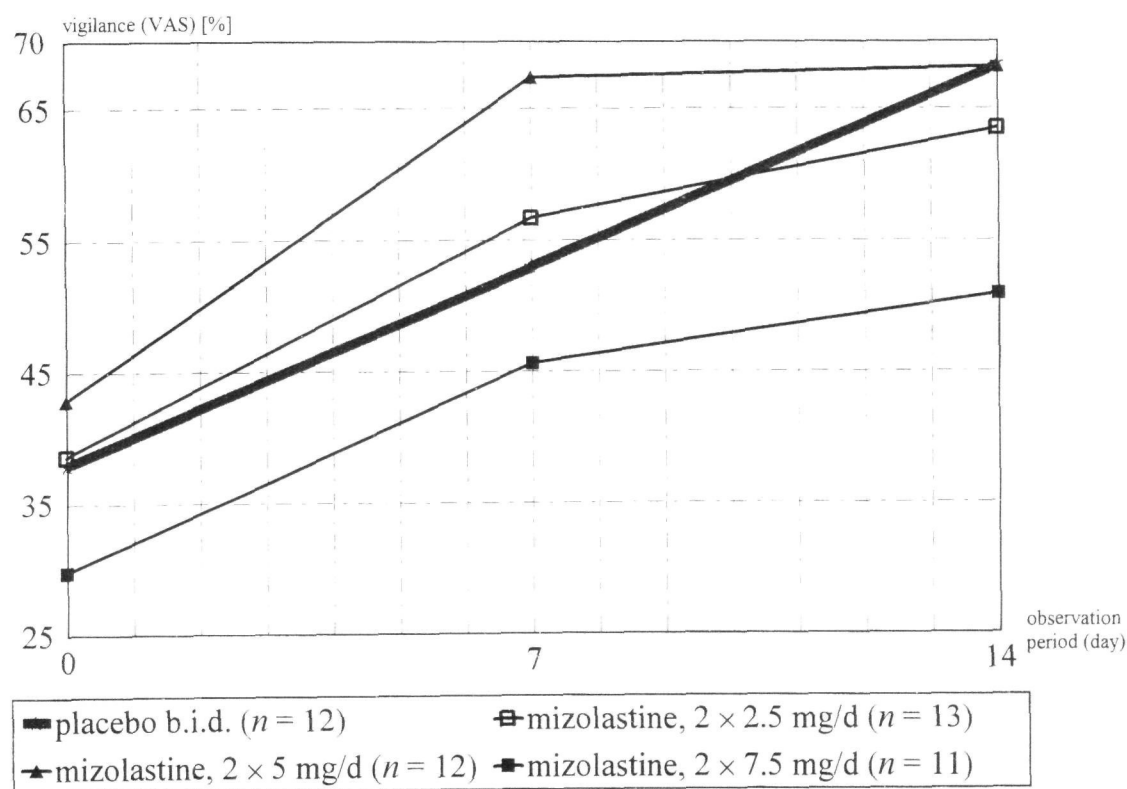
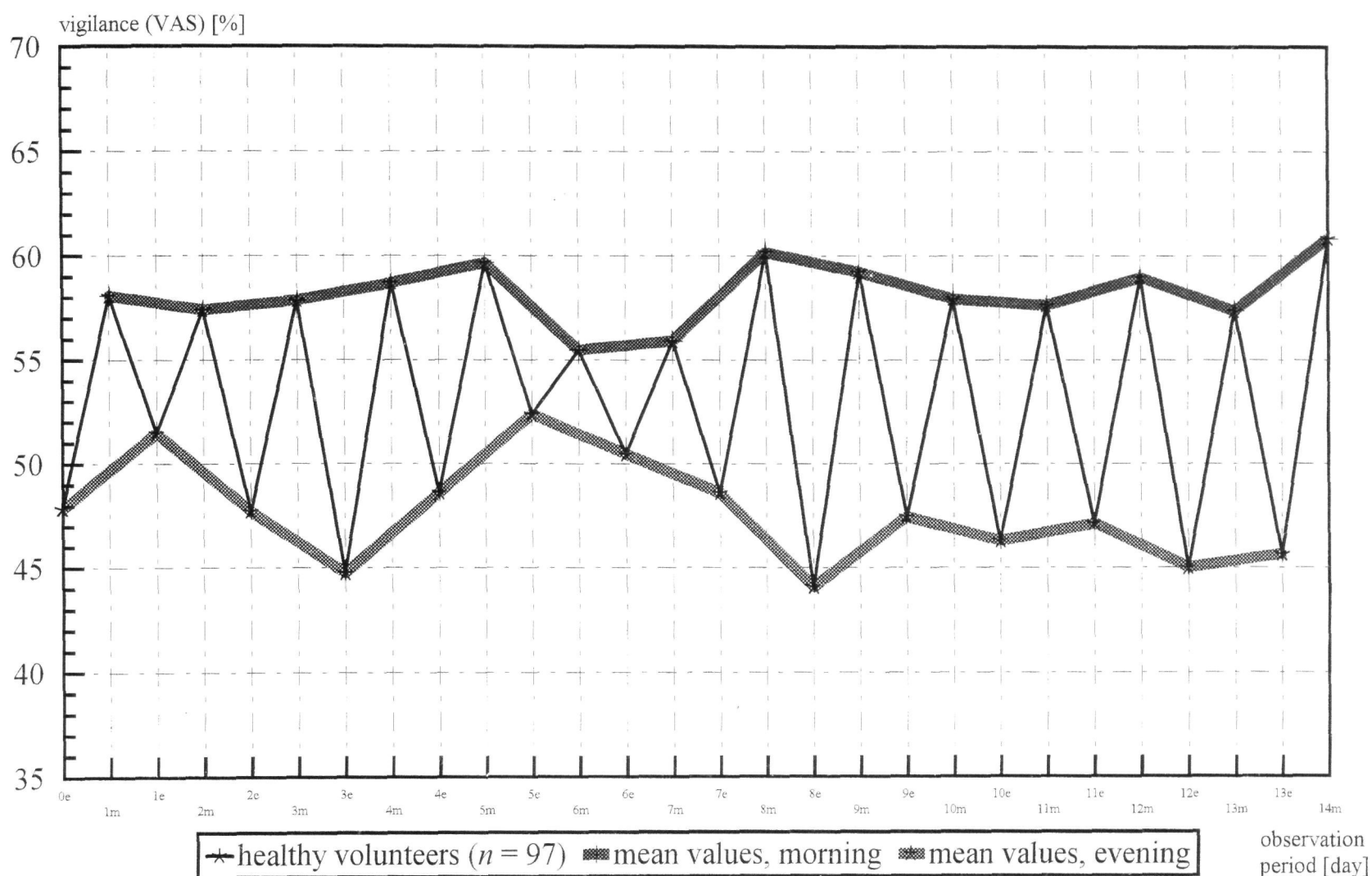
encompassing a number of studies with a total of several thousand patients, it was established that almost all of the examined compounds displayed a comparable sedation rate of 10–12% (9). This result applies to representatives of the early generations as well as to modern drugs. The large variation in individual values (0–20%) was striking. A mean sedation rate of 8% was established for the likewise examined placebos. In this meta-analysis, only loratadine showed a sedation rate below the rate for placebos. Therefore, there must be a complex interaction between histamine that is released from the mast cells in the course of an allergic reaction and the antihistaminic substrate that competes for the same central receptor. Only by a competitive inhibition of histaminergic sedation can we understand the potency of antihistamines to increase vigilance during treatment of symptomatic patients. In fact, different antihistamines obviously show more or less intrinsic activity. To investigate this mechanism, we performed a series of clinical trials with healthy volunteers as well as with patients suffering from allergic rhinitis either before or under treatment with an antihistamine.

Material and methods

The first study, which represents the baseline evaluation of vigilance, was performed in 1989 as a double-blind, placebo-controlled phase-II study with 48 patients in four parallel groups suffering from seasonal allergic rhinitis (Table 1). The presence of allergic disorder was verified by intracutaneous allergy testing and at least two “moderate” scores in the rhinoscopic evaluation of the rhinitis symptoms secretion, edema, and erythema. Treatment consisted of either one placebo tablet twice daily or 2.5, 5, or 7.5 mg of mizolastine (tablet)

Table 1. Clinical studies

Study, design (year)	Compound, route of administration, dosage	Patient no. (no. of diaries)	Ref.
d.-b., p.-c. (1989)	Mizolastine, tablet (2.5, 5, 7.5 mg b.i.d.); placebo, tablet	48 (48)	10
d.-b., d.-d. (1992)	Azelastine, spray (0.14 mg/puff/nostril b.i.d.) plus placebo, tablet	326 (277)	15
	Loratadine, tablet (10 mg) plus placebo, spray		
d.-b., d.-d. (1992)	Azelastine, spray (0.14 mg/puff/nostril b.i.d.) plus placebo, tablet	40 (37)	12
	Cetirizine, tablet (10 mg) plus placebo, spray		
d.-b., p.-c. (1992)	Azelastine, spray (0.14 mg/puff/nostril b.i.d.) plus placebo, tablet	60 (56)	11
	Azelastine, spray (0.14 mg/puff/nostril b.i.d.) plus azelastine, tablet (2 mg)		
d.-b., d.-d. (1994)	Azelastine, spray (0.14 mg/puff/nostril b.i.d.) plus placebo, tablet	296 (262)	
	Azelastine, spray (0.14 mg/puff/nostril b.i.d.) plus azelastine, tablet (2 mg)		
	Azelastine, tablet (2 mg) plus placebo, spray		
d.-b., p.-c. (1993)	Azelastine, spray (0.14 mg/puff/nostril b.i.d.) plus placebo, tablet/5d	300 (284)	14
	Azelastine, spray (0.14 mg/puff/nostril b.i.d.) plus azelastine, tablet (2 mg/5 d)		



b.i.d. Efficacy as well as tolerability was evaluated, a distinct advantage being shown by the verum already for the lowest dosage of 2.5 mg (10).

Sedative and similar effects were registered with two kinds of scales: the KUSTA (short scale of mood and activity) and the VAS. As the VAS was

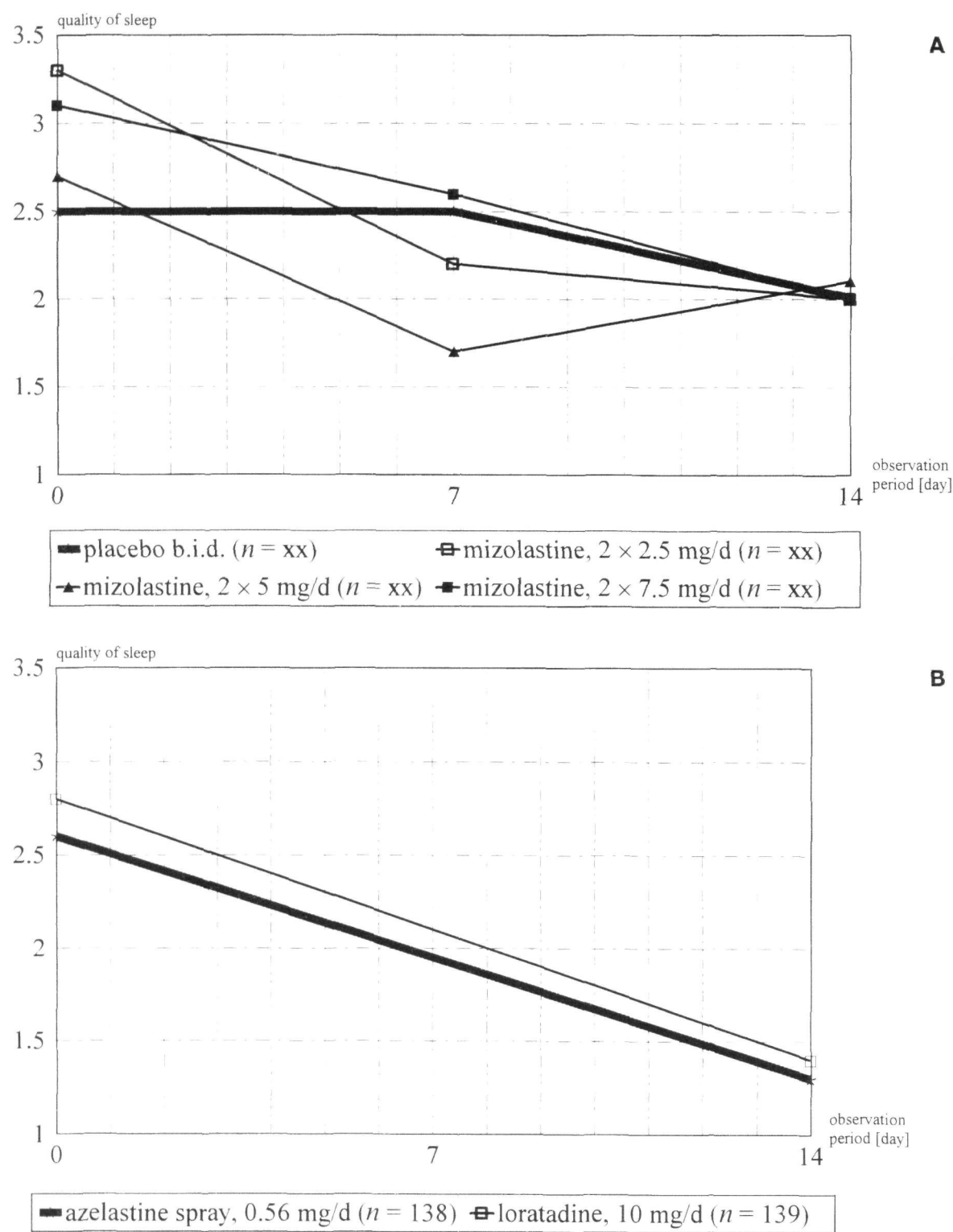


Fig. 3A. Quality of sleep in symptomatic patients suffering from allergic rhinitis under treatment with three doses of mizolastine (2×2.5, 5, or 7.5 mg, respectively) or placebo (twice daily). Daily registration of quality of sleep on scale (end points: 4=“very bad quality of sleep”, 0=“very good quality of sleep”) in diary.

Fig. 3B. Quality of sleep in symptomatic patients suffering from allergic rhinitis under treatment with azelastine nasal spray (2×0.14 mg/nostril/day) or loratadine (10 mg, taken in morning). Daily registration of quality of sleep on scale (end points: 4=“very bad quality of sleep”, 0=“very good quality of sleep”) in diary.

also used in the following studies, its results obtained from three visits to the investigator (days 0, 7, and 14) were the basis for later investigation. The principle of this method is a horizontal line of 10 cm. The ends of this line represent either the best or worst condition of vigilance (“feeling wide awake” or “feeling extremely tired”). The patient’s mark on this line is calculated to the percentage of the total length, resulting in a value between 0 and

100%. Thus, the meaning of this value depends on the position of the two statements on the right and left sides. For comparability of our results, the “100%” value always represents the optimum condition of the patient’s vigilance. Finally, in the course of this trial, the quality of sleep was assessed on days 0, 7, and 14 with a four-step ordinal scale (0=“very good quality of sleep”, 4=“very bad quality of sleep”).

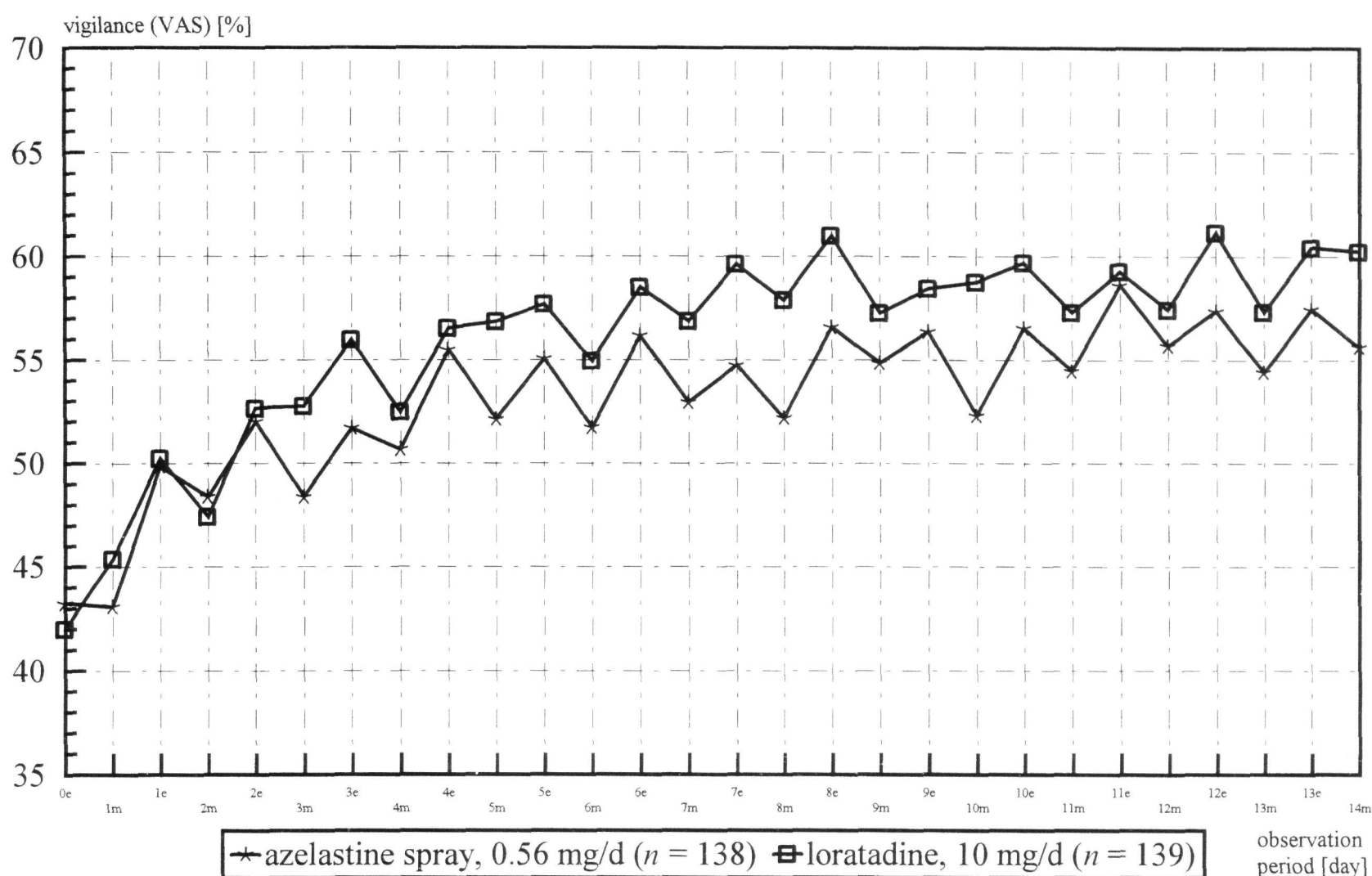


Fig. 4. Course of vigilance in symptomatic patients suffering from seasonal allergic rhinitis in double-blind comparison of azelastine nasal spray (2×0.14 mg/nostri/day) and loratadine (10 mg, taken in morning). Twice daily registration of vigilance on visual analog scale (VAS; end points: 100% = "wide awake", 0% = "extremely tired") in diary (m = morning, e = evening).

The results obtained from a series of clinical phase-IV studies were the basis of our further investigation (Table 1). During these controlled, randomized, double-blind studies, the new antihistamine azelastine was compared to oral compounds of the same substance class (H_1 -antagonists). Azelastine is the only agent of that group which is currently available as nasal spray and in an oral formulation. Its efficacy has been verified in placebo-controlled studies before its drug registration. Different types of application (oral/topical) as well as different doses (one or two puffs of azelastine nasal spray) were also examined in order to identify effects depending on these factors. Patients suffering from seasonal allergic rhinitis and partially also from perennial rhinitis were selected. A skin prick or intracutaneous test verified the allergic reaction in all cases. At the time of testing, severe symptoms were present, as rated by the examiner by means of a symptoms score. A minimal sum score (at least two "moderate" scores in the evaluation of the rhinitis symptoms obstruction, secretion, sneezing, and itching) was required. The results of the individual clinical studies as well as statistical methods applied, all other inclusion criteria, and permitted concomitant

medication are described in earlier publications (11–15).

For detection of a possible sedative effect resulting from treatment, a diary was given to the patient during the 2- or 4-week study period. Herein patients documented not only the intensity of their complaints before medication administration in the morning and in the evening, but also noted their vigilance on a VAS between the limiting values of "extremely tired" and "wide awake". These entries were averaged over the respective patient group and recorded on a chart.

Finally, during the pollen season in 1995, we asked 97 healthy persons to state their vigilance on an identical VAS in the morning and evening over a period of 2 weeks. Demographic data were comparable to those of the patients of the previous studies.

The unpaired *t*-test was used to calculate the statistical significance of the differences of vigilance determined by the VAS.

Results

Fig. 1 shows the results obtained during 2 weeks in the pollen season from healthy persons, who can

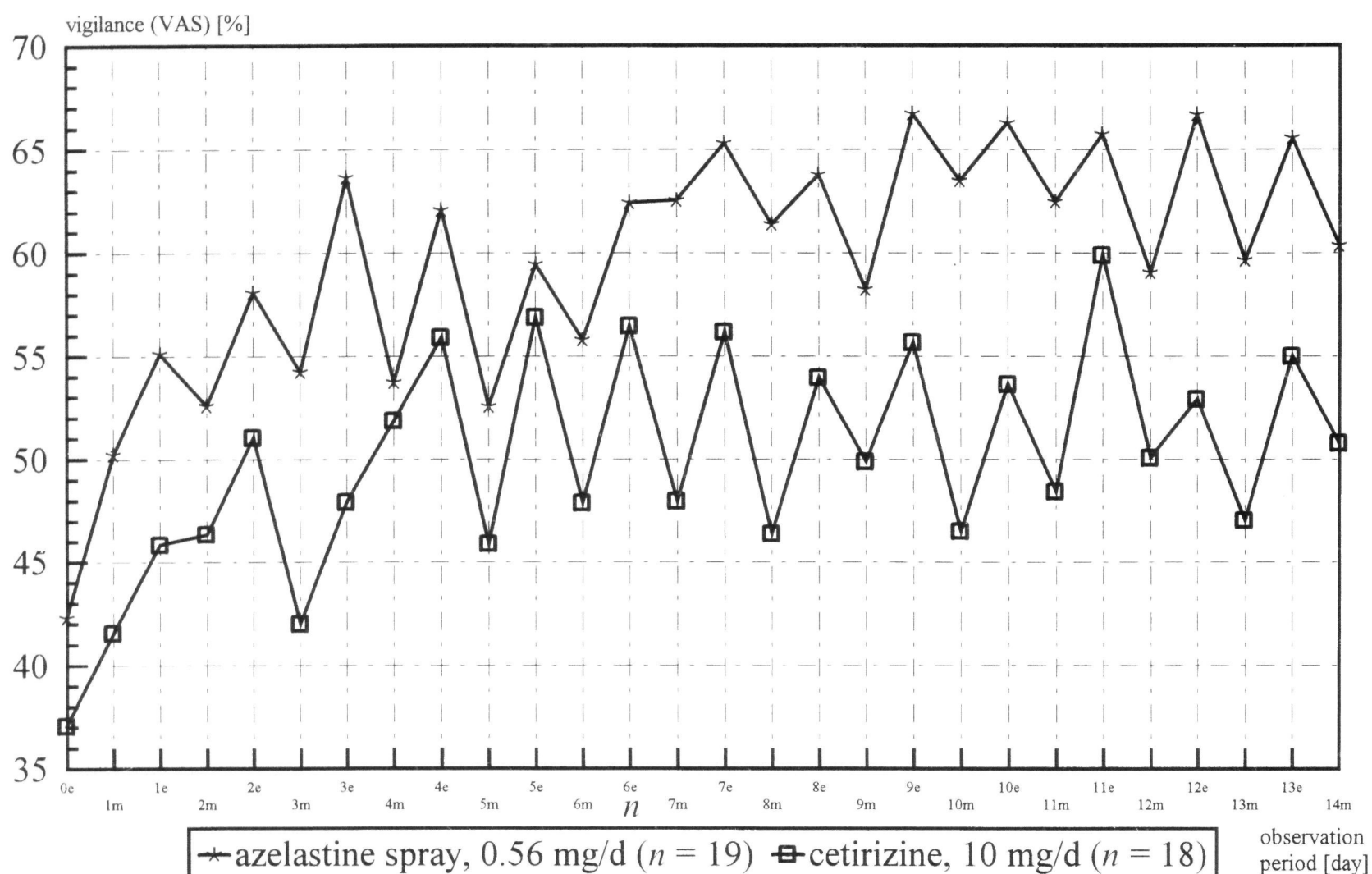


Fig. 5. Course of vigilance in symptomatic patients suffering from seasonal allergic rhinitis in double-blind comparison of azelastine nasal spray (2×0.14 mg/nostril/day) and cetirizine (10 mg, taken in morning). Twice daily registration of vigilance on visual analog scale (VAS; end points: 100% = "wide awake", 0% = "extremely tired") in diary (m = morning, e = evening).

be regarded as a control group ($n = 97$). The time and design of this investigation were determined in order to guarantee comparable conditions for the subsequently presented clinical studies. The mean daily values $\pm$ standard deviation ranged between $44.07\% \pm 23.22\%$ and $60.82\% \pm 21.59\%$, representing the actual vigilance in the morning and evening. We found a marked circadian rhythm of vigilance with a maximum constantly being found in the morning. Differences between morning and evening values ranged from 3.1% to 16.1%, and the mean difference between the mean values (morning: 58.22%; evening: 47.67%) was 10.47%. There was no significant increase or decrease of vigilance over the whole period of registration.

The starting level of VAS scores from the patients treated with mizolastine or placebo (double-blind, placebo-controlled study; $n = 48$) proves that due to the effects of the allergic disorder, vigilance fell to distinctly lower levels. Before starting treatment, patient assessment of vigilance ranged between $29.7\% \pm 5.4\%$ and $42.8\% \pm 6.2\%$. In the first week, scores significantly rose under treatment with verum as well as with placebo ($P < 0.0001$ for all groups), but for mizolastine the improvement was

consistently more distinct for either dosage, VAS scores almost reaching their definitive level on day 7 (Fig. 2). Subsequently, there appeared only little or no further significant change during the second half of the treatment period for those patients (2.5 mg: $P = 0.0014$; 5 mg: $P = 0.6538$; 7.5 mg: $P = 0.0812$). In contrast, for placebo, we found a continuous significant increase until the end of treatment ($P < 0.0001$ for the second week), a finding that has to be discussed later. Simultaneously, quality of sleep distinctly improved in the three verum groups during the first week of treatment, whereas there was only a slight change in the second week in the placebo group (Fig. 3A).

A total of 916 diaries from 1022 patients, who took part in five controlled, double-blind studies during the pollen seasons of 1992, 1993, and 1994, were the object of further evaluation. The therapeutic efficacy of the compound under investigation, azelastine, had been proved in several previous placebo-controlled, clinical studies (16–18). The reference compounds had previously shown their therapeutic potency (12, 15, 19).

For most patients, the VAS showed an increase in vigilance during treatment independently

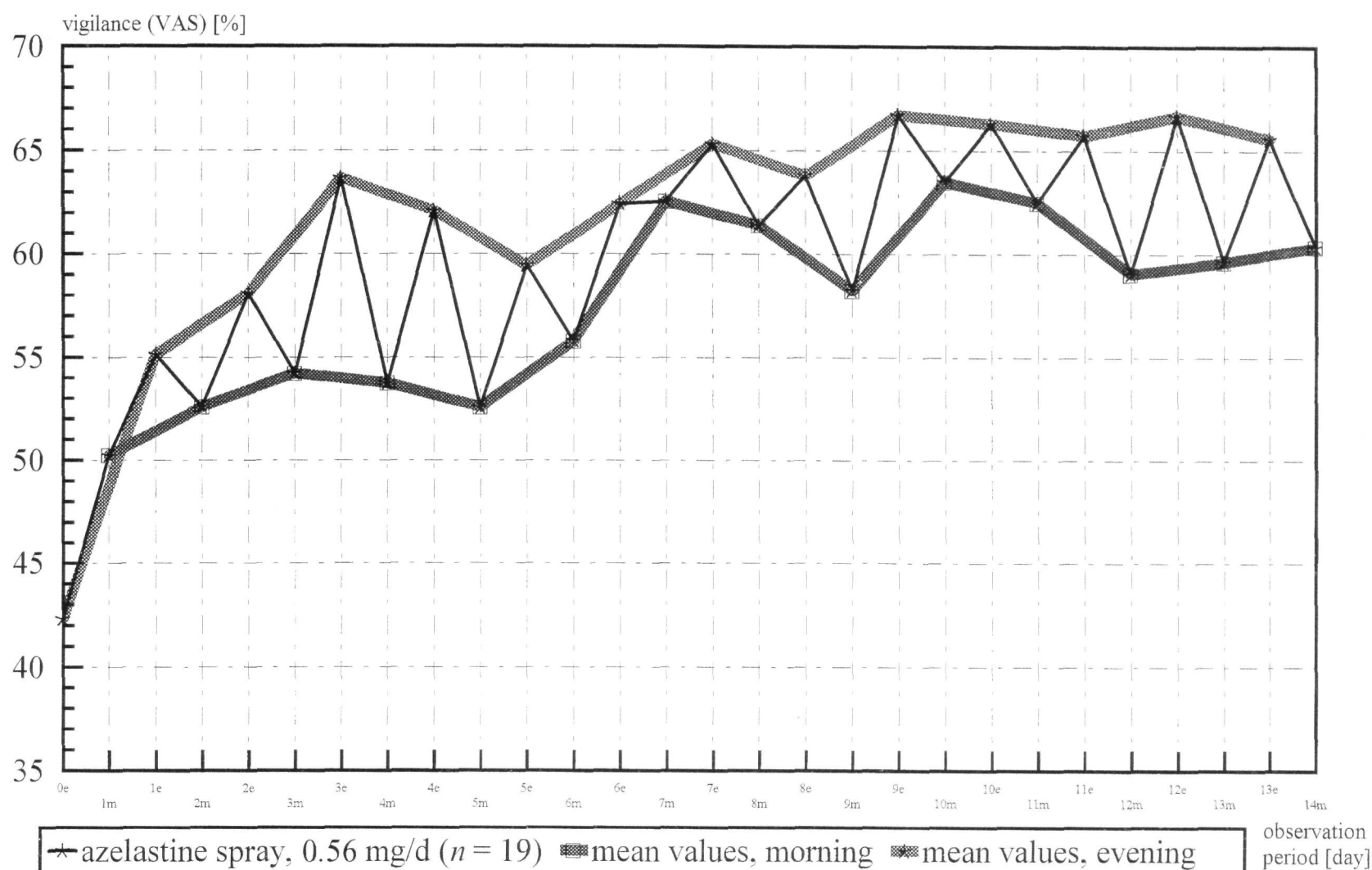


Fig. 6. Course of vigilance and less pronounced circadian variation of vigilance in symptomatic patients suffering from seasonal allergic rhinitis under topical antihistamine treatment with azelastine nasal spray (2×0.14 mg/nostril/day). Bold lines refer to mean morning and evening values, respectively. Twice daily registration of vigilance on visual analog scale (VAS; end points: 100% = "wide awake", 0% = "extremely tired") in diary (m = morning, e = evening).

of the administered drug. This was confirmed by the evaluation of the vigilance for each therapy group (topical and systemic therapy) with the compounds azelastine, cetirizine, loratadine, and astemizole. Nevertheless, differences between the individual compounds became apparent.

Figs. 4–10 show the mean values obtained for each therapy group of these randomized, double-blind studies by rating patient condition on a VAS in the morning and in the evening. Fig. 4 summarizes a comparative double-blind study by the double-dummy technique in 326 patients. A total of 138 patients who administered 0.14 mg azelastine nasal spray into both nostrils twice a day and 139 patients who took loratadine tablets (10 mg, in the morning) made entries in their diaries over a treatment period of 14 days ("intent-to-treat" analysis). The increase in vigilance on the VAS from day 1, with a mean value (MV) of 43% (standard deviation = SD: $\pm 20\%$) for azelastine and 42% (SD: $\pm 19\%$) for loratadine until day 14 and an MV of 57% (SD: $\pm 20\%$) for azelastine and 60% (SD: $\pm 21\%$) for loratadine, was distinct and statistically significant ($P < 0.0001$) for both preparations.

Fig. 5 summarizes a double-blind study with 40 patients, in which the topical therapy with azelastine nasal spray (one puff = 0.14 mg/nostril b.i.d.) was compared to systemic therapy with cetirizine tablets (10 mg, taken in the morning) by the double-dummy technique. In this case, 19 diaries of the azelastine group and 18 diaries of the cetirizine group were evaluable. For azelastine, a development in vigilance was displayed which was almost identical to the above described curves (day 1: MV: 42%, SD: $\pm 18\%$; day 14: MV: 65%, SD: $\pm 14\%$; $P < 0.0001$). This positive trend, though markedly less pronounced ($P = 0.0254$), could also be observed for cetirizine (day 1: MV: 37%, SD: $\pm$; day 14: MV: 55%, SD: $\pm 25\%$). Especially striking was the distinct circadian variation, with a vigilance minimum in the morning in the case of systemic application of the drug (Figs. 6 and 7). This corresponds well to a significant difference in sedation between azelastine nasal spray and cetirizine tablets reported from another double-blind trial (19).

Fig. 8 shows the vigilance scores of a double-blind, controlled trial in two patient groups ($n = 60$) being treated with azelastine nasal spray (one

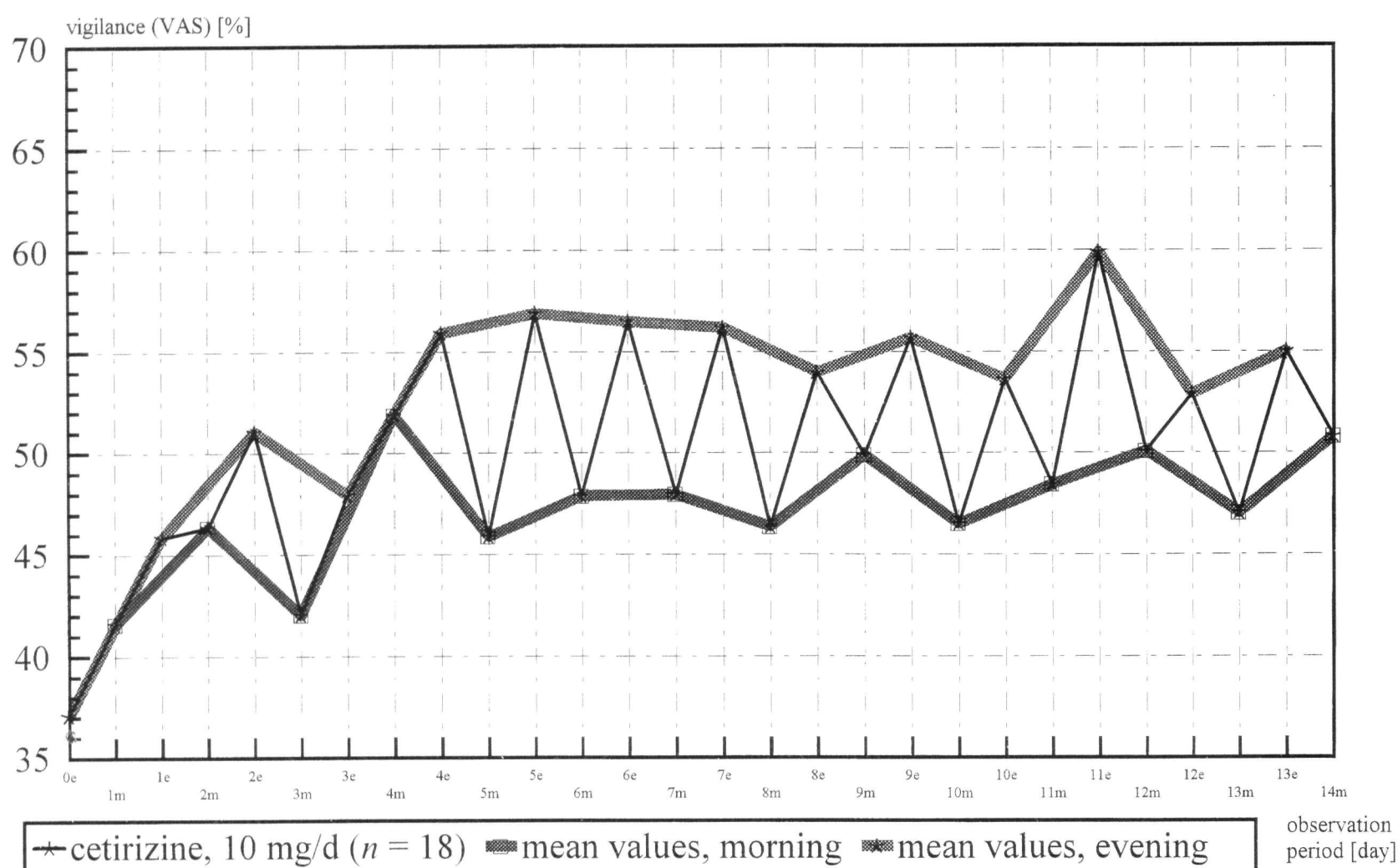


Fig. 7. Course of vigilance and distinct circadian variation of vigilance in symptomatic patients suffering from seasonal allergic rhinitis under systemic antihistamine treatment with cetirizine (10 mg, taken in morning). Bold lines refer to mean morning and evening values, respectively. Twice daily registration of vigilance on visual analog scale (VAS; end points: 100% = "wide awake", 0% = "extremely tired") in diary (m = morning, e = evening).

puff = 0.14 mg/nostril b.i.d.) and additionally either an azelastine tablet (2 mg, taken in the evening) or a placebo tablet. The data from 28 patients of both groups were as follows: combination of azelastine nasal spray and tablets day 1: MV: 43%, SD: $\pm 25\%$; day 14: MV: 52%, SD: $\pm 37\%$; azelastine nasal spray and placebo tablet: MV: 37%, SD: $\pm 29\%$; day 14: MV: 49%, SD: $\pm 35\%$. These results are in line with the previous results. However, improvement was not significant for both groups (combination: $P = 0.2628$; spray: $P = 0.1409$), as the level for the VAS scores in these patients suffering from severe mixed seasonal and perennial allergic rhinitis appeared to be lower than in other trials. Again, systemic treatment caused a distinct circadian variation.

The graphs displayed in Fig. 9 show the results of a double-blind, double-dummy study with three parallel groups ($n = 296$) comparing combined therapy (azelastine nasal spray [one puff = 0.14 mg/nostril b.i.d.] and one tablet [2 mg, taken in the evening]; $n = 89$ diaries) and monotherapy (azelastine nasal spray [one puff = 0.14 mg/nostril b.i.d.] and one placebo tablet; $n = 85$ diaries), as performed in the previous study with monotherapy with two azelastine tablets (2 mg, taken in the

morning and the evening; $n = 88$ diaries combined with a placebo nasal spray). In this case, therapy lasted 4 weeks. For all therapy groups, we found a significant improvement in vigilance, but for patients being treated with spray (combined or monotherapy) this increase was distinctly more pronounced than with the verum tablets alone (combination of azelastine nasal spray and tablet: day 1: MV: 46%, SD: $\pm 19\%$; day 28: MV: 58%, SD: $\pm 23\%$; $P = 0.0009$; azelastine nasal spray and placebo tablet: day 1: MV: 43%, SD: $\pm 21\%$; day 28: MV: 58%, SD: $\pm 22\%$; $P < 0.0001$; azelastine tablets and placebo nasal spray: day 1: MV: 43%, SD: $\pm 21\%$; day 28: MV: 55%, SD: $\pm 22\%$; $P = 0.0005$). After reaching a level of high vigilance scores (days 7–9), we recorded an inverse circadian rhythm in the group with combined treatment that was comparable to the results of the control group (Fig. 1). This development could not be seen as clearly in any other therapy group, as, especially in the first 2 weeks of treatment, patients receiving only verum monotherapy showed the slight undulations known from all other investigations.

Finally, Fig. 10 shows the results obtained from another double-blind study by the double-dummy technique ($n = 300$), comparing the combination of

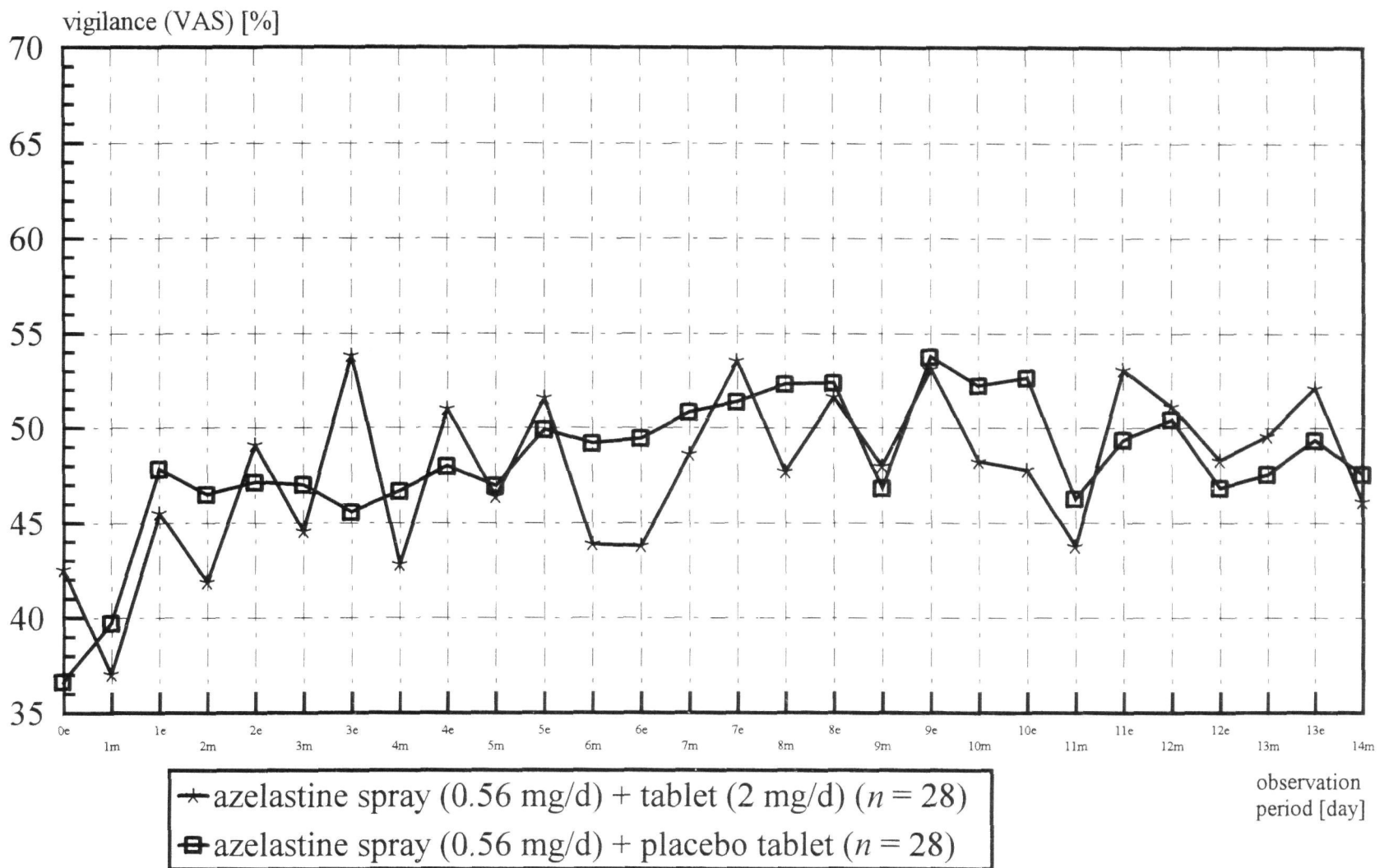


Fig. 8. Course of vigilance in symptomatic patients suffering from perennial allergic rhinitis in double-blind comparative study of azelastine nasal spray (2×0.14 mg/nostril/day) in combination with either one azelastine tablet (2 mg, taken in evening) or one placebo tablet, showing marked difference in circadian variation of vigilance between topical (nasal) and systemic (combined) antihistamine treatment. Twice daily registration of vigilance on visual analog scale (VAS; end points: 100% = "wide awake", 0% = "extremely tired") in diary (m = morning, e = evening).

azelastine nasal spray with either one azelastine tablet (2 mg, taken in the evening) or a placebo tablet ($n = 142$ diaries, respectively). The additional tablet was only given during days 1–5 of treatment with azelastine nasal spray. Again, the increase in vigilance for both therapy groups (combination of azelastine nasal spray and tablet: day 1: MV: 42%, SD: $\pm 19\%$; day 14: MV: 61%, SD: $\pm 17\%$; azelastine nasal spray and placebo tablet: MV: 39%, SD: $\pm 21\%$; day 14: MV: 59%, SD: $\pm 18\%$) was evident and statistically significant ($P < 0.0001$). For the patients being treated with nasal monotherapy, we found no difference between morning and evening scores, whereas a circadian undulation in vigilance levels could be seen in patients taking an additional verum tablet.

Discussion

In the past, antihistamines were generally believed to be drugs with strong antiallergic potency but undesirable sedative effects. Since a new generation of antihistamines for systemic, and at last also for topical, application has been developed, this

picture has completely changed. The results obtained from a phase-II study in 1989 first indicated this, since mizolastine proved to be superior to placebo in its sedative score from patient ratings in the VAS (10). Meanwhile the recommended dose for this substance has been set at 10 mg o.d. due to the good result for the group receiving 5 mg b.i.d. The improvement in quality of sleep that could be documented simultaneously for the patients who received verum explains this favorable trend. The results for the placebo group with a slow and steady improvement in all parameters has to be seen in the light of decreasing allergen exposure at the end of the pollen season, since this trial was carried out from June to September. Consequently, any differences in vigilance between placebo and verum were found during the first days of treatment, whereas the trend to improved final scores was the same for all treatment groups.

A similar improvement has now been observed in our studies with azelastine nasal spray, azelastine tablets, and several other oral antihistamines. The values for the new "nonsedating antihistamines" fall below the sedation rates for placebo (3). This

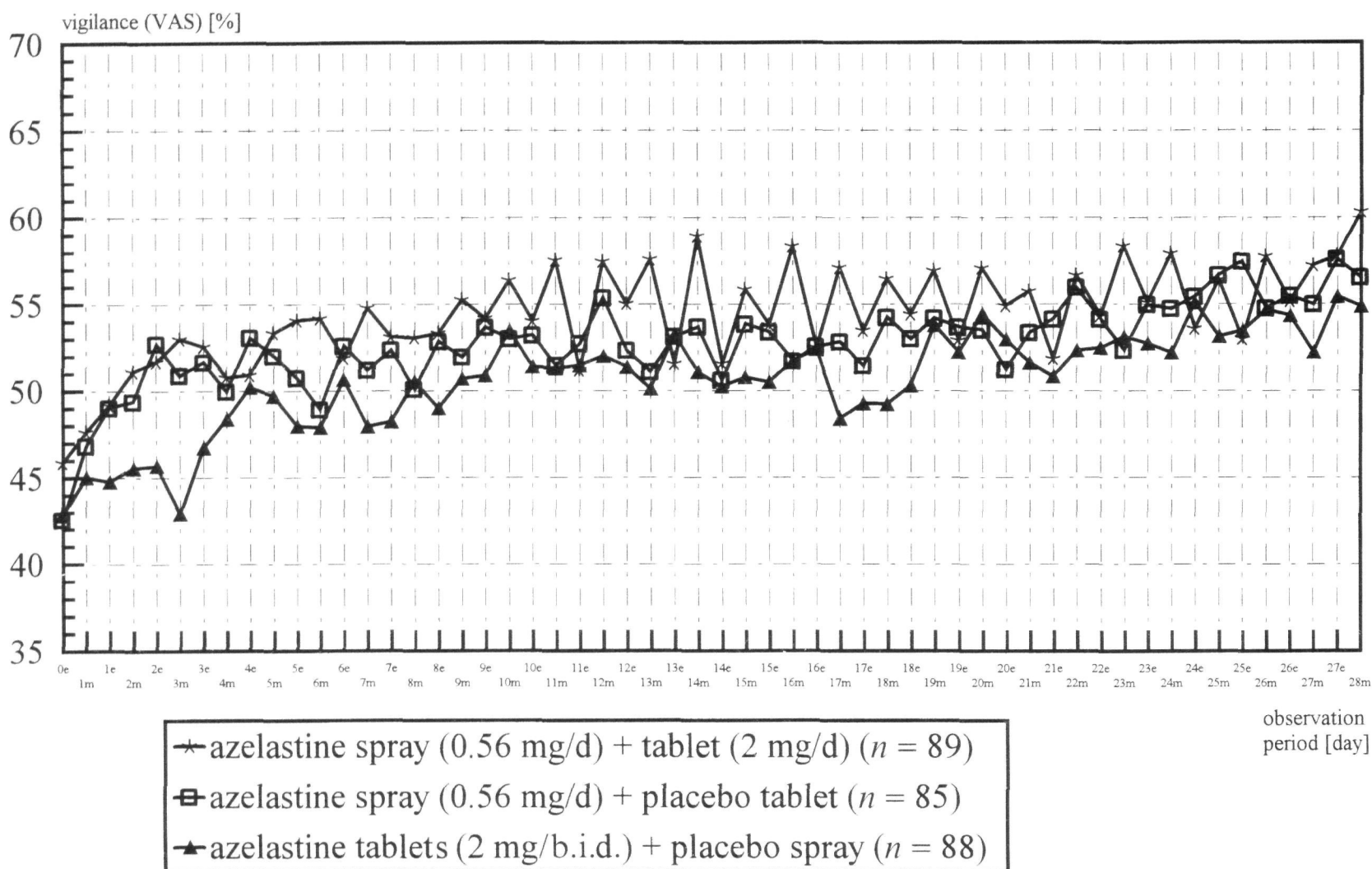


Fig. 9. Course of vigilance in symptomatic patients suffering from seasonal allergic rhinitis in double-blind comparison of azelastine nasal spray (2×0.14 mg/nos-tril/day plus one placebo tablet), two azelastine tablets (2 mg, taken in morning and evening plus placebo nasal spray twice daily), and combination of azelastine nasal spray and tablet (dosages as shown above). Twice daily registration of vigilance on visual analog scale (VAS; end points: 100% = "wide awake", 0% = "extremely tired") in diary (m = morning, e = evening).

indicates that vigilance increases during treatment, a finding which requires an explanation.

At first sight, it is not comprehensible that a compound used in drug treatment should show fewer side-effects than a pharmacologically inert placebo. Two factors influence the level of vigilance of our patients. On one hand, we find effects resulting directly from the disorder, such as nasal obstruction and bronchial symptoms with sleep disorders. In addition to this, the allergic patient's tolerance of symptoms is highly variable among individual patients (20). A pharmacologically induced sedation can possibly also be observed, worsening the condition and vigilance of allergic patients. On the other hand, counter-acting effects result from efficient antiallergic treatment, with a prevalent exclusion of symptoms as well as a natural or random allergen reduction.

The sum of these effects determines the actual condition of the allergic patient, which is also reflected by psychometric data used for the evaluation of sedation. The interaction of disorder, treatment, effects, and side-effects has a

substantial influence on the sedation value measured by VAS. Therefore, pharmacologic side-effects were not rated in these studies but rather a summation effect in which sedation was only one factor. Nevertheless, in previous studies that compared the sedative effects of selected antihistamines by objective parameters, only little or no effect on central nervous system function or everyday activities occurred (1, 21). This can also be confirmed for two of the compounds of the present studies – loratadine and cetirizine – which showed comparable negligible sedative effects either in objective tests in healthy volunteers or in subjective measurements such as VAS in symptomatic patients using equal doses of the drugs. The favorable outcome of the studies for the investigated antihistamines in comparison to placebo can be interpreted only in this manner.

Our above explained hypothesis can be verified by the evaluation of a quality-of-life questionnaire (22). Data were obtained from 231 patients of the study comparing azelastine nasal spray and loratadine tablets. The increase in vigilance for both

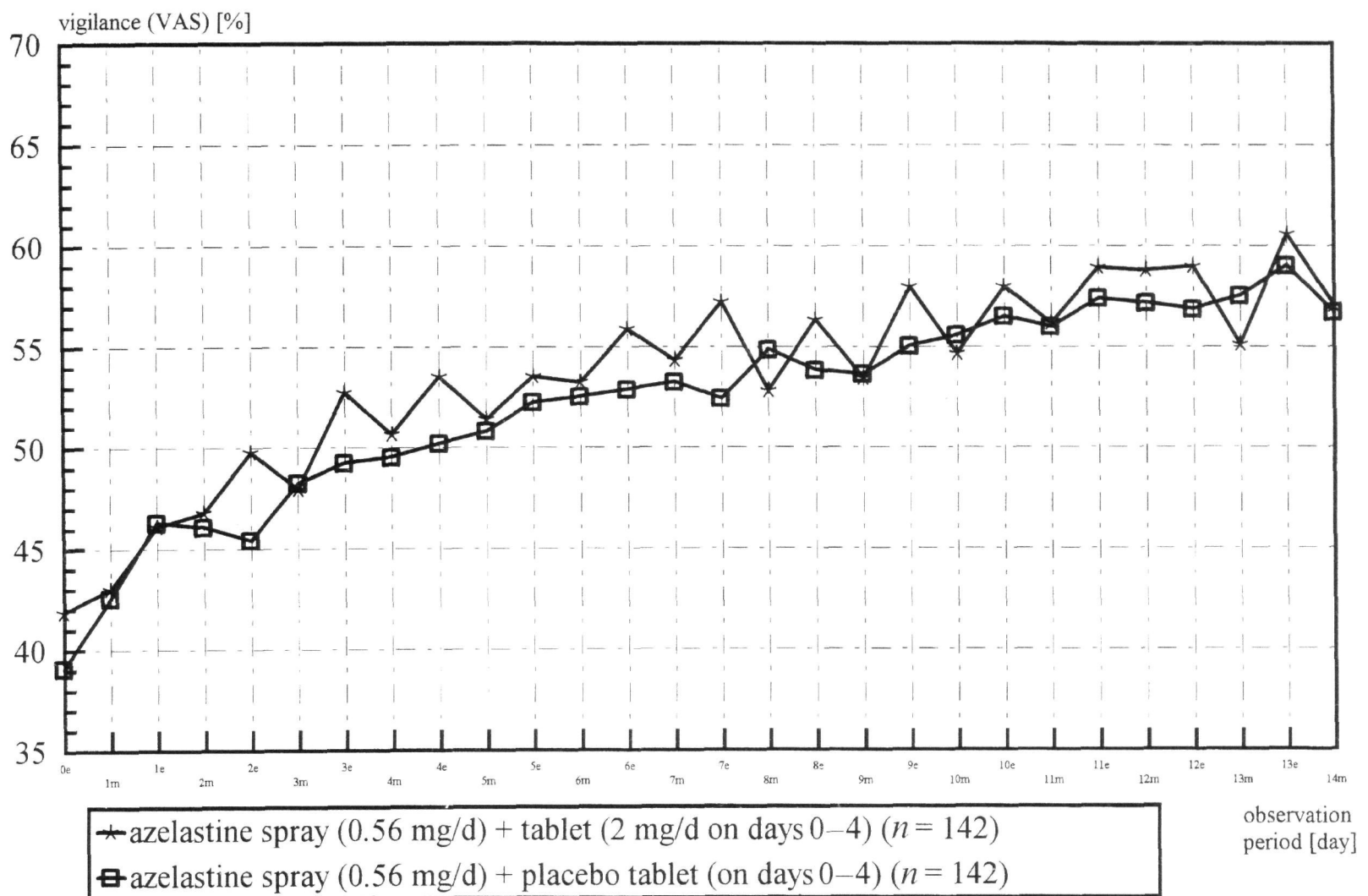


Fig. 10. Course of vigilance in symptomatic patients suffering from seasonal allergic rhinitis in double-blind comparative study of azelastine nasal spray (2×0.14 mg/nostril/day) combined with either one azelastine tablet (2 mg, taken in evening) or one placebo tablet for days 1–5 of study, showing improvement of vigilance during daytime under additional treatment with “sedative” oral compound. Twice daily registration of vigilance on visual analog scale (VAS; end points: 100% = “wide awake”, 0% = “extremely tired”) in diary (m = morning, e = evening).

therapy groups shown in Fig. 4 is, to an important extent, the result of a significant improvement in quality of sleep ($P < 0.0001$) (azelastine: day 1: MV: 2.6, SD: ± 1.5 ; day 14: MV: 1.3, SD: ± 1.2 ; loratadine: MV: 2.8, SD: ± 1.6 ; day 14: MV: 1.4, SD: ± 1.2). This aspect had already become apparent in the mizolastine study in 1989 (Fig. 3B). Furthermore, a positive trend could be registered in all scores dealing with general quality of life.

Another striking result of the studies was a more or less marked difference in the daily course of vigilance for either oral or topical administration. Patients who were treated with azelastine nasal spray usually did not show a marked increase during daytime but significantly improved over the whole period of treatment (Fig. 11). In contrast, most of the oral compounds investigated were characterized by a vigilance minimum in the morning and a maximum in the evening independently of the time of intake of the drug (morning or evening). However, we admit that Fig. 10 requires further explanation. The VAS rating in the group receiving combined nasal and, only for days 1–5 of

the study, additional oral treatment with azelastine did not change after day 5 when additional administration of a verum tablet stopped. In fact, the mean values of daily vigilance decreased under monotherapy after day 5 and showed a regression to the values of the group treated with azelastine nasal spray for the entire study period (additional placebo tablet during the first 5 days).

The fact that drug therapy causes an undulation that is inverse to the natural course displayed in Fig. 1 requires special attention and further explanation. On the one hand, it is evident that the differences between morning and evening scores were much less than in the control group. On the other hand, one has to bear in mind how the statements on the VAS were formulated. In most of the clinical trials, patients were asked about their condition in the past 12 h, whereas the members of the control group were asked how they felt at the time of rating on the VAS. This might explain why part of the graphs displayed in Fig. 9 show a course that is similar to physiologic conditions, since the VAS statements of this study were identical to

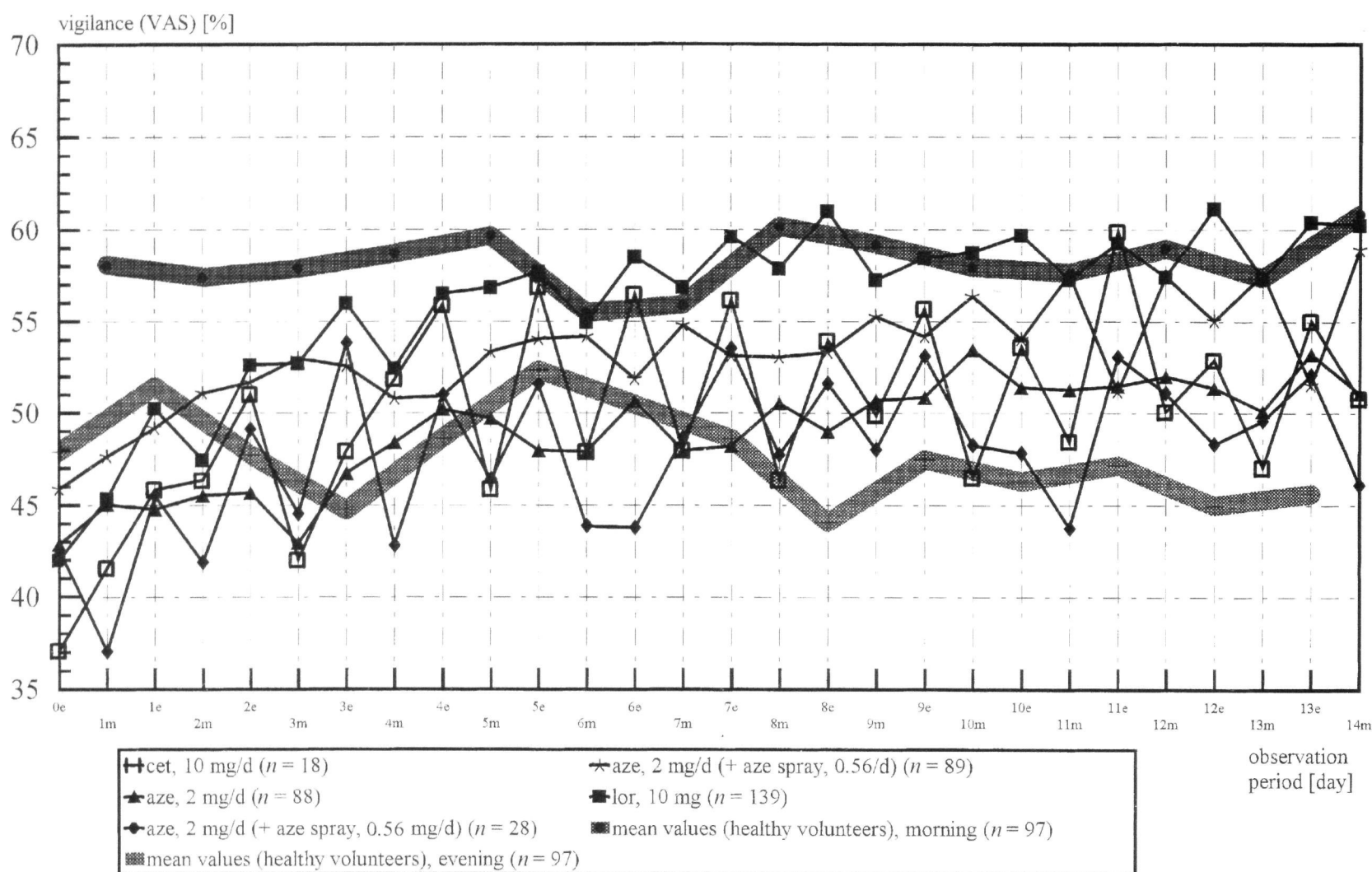


Fig. 11. Course of vigilance in symptomatic patients suffering from allergic rhinitis under treatment with different oral antihistamines. Bold lines refer to mean morning and evening values of healthy volunteers, respectively. Twice daily registration of vigilance on visual analog scale (VAS; end points: 100% = "wide awake", 0% = "extremely tired") in diary (m = morning, e = evening, cet = cetirizine, aze = azelastine, lor = loratadine).

those used for the control group. Nevertheless, all scores of any of the examined drugs lie within the ranges defined by the control group (Figs. 11 and 12). In conclusion, this means that, due to reduced circadian rhythm, patients stabilized on a level of vigilance that was significantly higher than before or without sufficient treatment and at least in the range of healthy persons.

Regarding the effects which can be seen under antihistamine treatment, another point arises: if improvement of vigilance was a result of different pharmacologic and physiologic effects, we could expect similar trends under treatment with drugs such as glucocorticoids, imidazoles, or cromoglycates. Possibly further investigations with other substances on this topic could also help us to understand the meaning of circadian variation in vigilance which is characteristic of antihistamine treatment.

Finally, the treatment of patients suffering from seasonal or mixed seasonal/perennial allergic rhinitis involves the following considerations:

- 1) The basis of efficient treatment must be allergen avoidance. Depending on the specific allergen, this measure is only practicable to some extent. However, the patient should be informed of this

measure during counseling; e.g., by mentioning the pollen warning service.

- 2) In pharmacologic antiallergic treatment, topically or systemically applied antihistamines represent highly specific and virtually nonsedating compounds of first choice (23). We found the most obvious improvement in vigilance of our patients during treatment with loratadine and azelastine. During treatment with cetirizine, this improvement was still detectable. Thereafter, our results for sedation or sleepiness are quite comparable to those of spontaneous reports of adverse reactions in clinical practice (24). For all oral antihistamines subject to our trials, we can confirm a more or less marked circadian variation in vigilance. This observation deserves special attention, as the period of maximum benefit for the patients is found during daytime. Therefore, if sedative effects occur at all, they do not seem to interfere with daily routine (e.g., work, driving) but coincide with the time of sleep. Subsequently, an inadequately treated patient poses a greater risk – e.g., in traffic – than a symptom-free allergy patient treated with an antihistamine. However, in every patient group, there were patients who

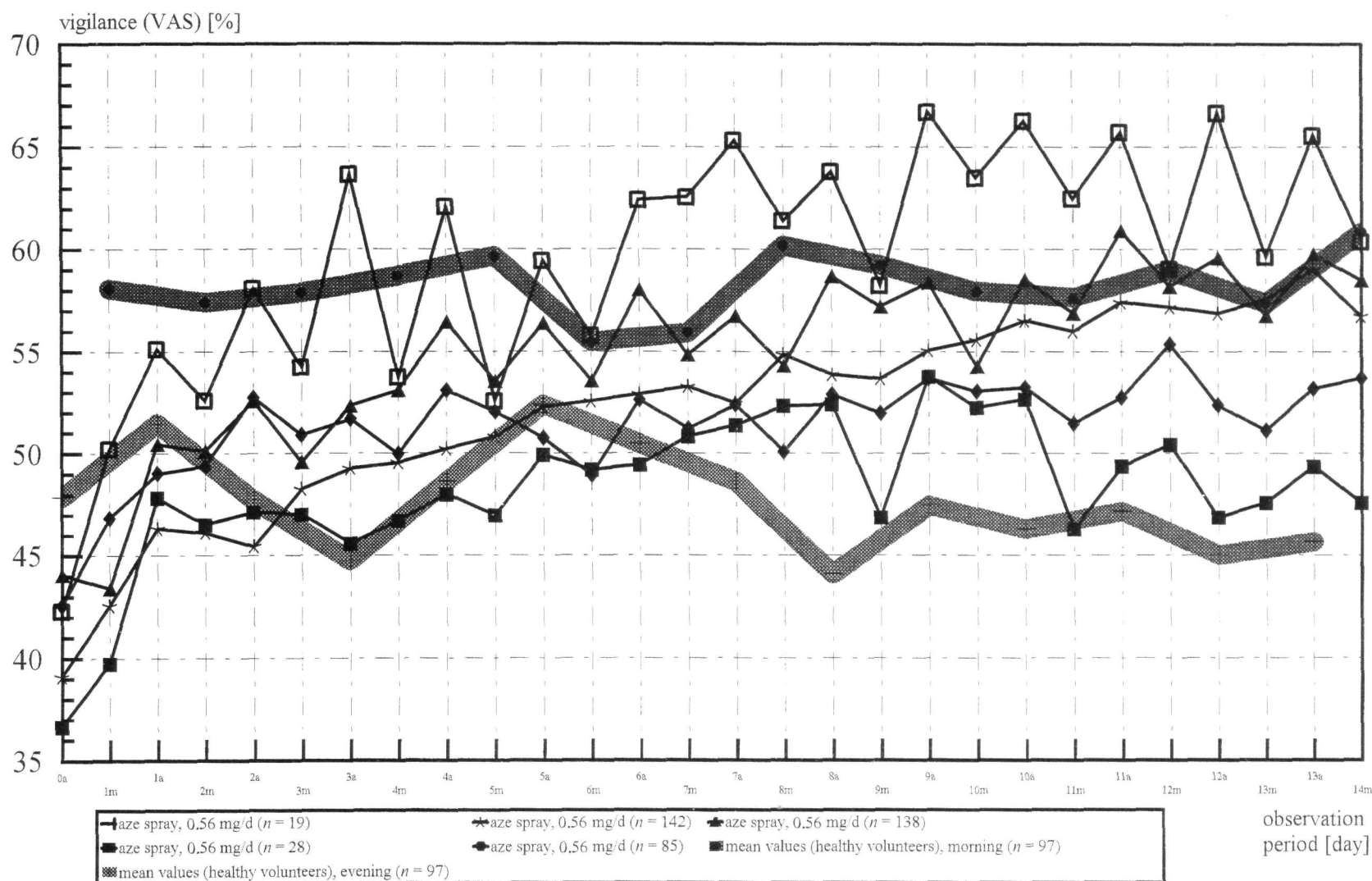


Fig. 12. Course of vigilance in symptomatic patients suffering from allergic rhinitis under treatment with azelastine nasal spray (2×0.14 mg/nostril/day) in different studies. Bold lines refer to mean morning and evening values of healthy volunteers, respectively. Twice daily registration of vigilance on visual analog scale (VAS; end points: 100% = "wide awake", 0% = "extremely tired") in diary (m = morning, e = evening, aze = azelastine).

complained of extensive sedation. The great range of the registered levels of vigilance underlines this statement. Finally, therapy with an antihistamine has to respect the individual risk-benefit ratio of every patient and therefore sometimes requires testing of different drugs.

For an exact evaluation of sedation in clinical therapeutic studies, it is necessary to employ adequate objective tests. Until now, these tests have been used only in studies with volunteers. According to our studies, an isolated investigation of the central sedative effects on healthy persons alone, without consideration of the clinical picture, must be inconclusive.

References

- Hindmarch I. Psychometric aspects of antihistamines. *Allergy* 1995;50 Suppl 24:48-54.
- Schmutzler W. Mediatorensysteme – Biochemie und Pharmakologie. In: Fuchs E, Schulz KH, editors. *Manuale allergologicum*. München-Deisenhofen: Dustri-Verlag Dr K Feistle, 1988.
- Spaeth J, Mösges R, Klimek L. Non-sedating antihistamines – fact or fiction? *Allergologie* 1994;17:204-7.
- Becker-Brüser W, editor. Müdigkeit nach Antiallergikum Azelastin (Allergodil®). *Arzneimitteltelegramm* 1993;7.
- Bhatti JZ, Hindmarch I. Antihistamines and car driving. In: O'Hanlon JF, Debier JJ, editors. *Drugs and driving*. London: Taylor & Francis, 1986.
- Alford C, Bhatti JZ, Rombaut NEI, Curran S, Hindmarch I. A comparison of antihistamines using EEG and questionnaire based assessment. *Med Sci Res* 1989;17:420-3.
- Wendt G, Binz U. Die KUSTA (Kurz-Skala Stimmung/Aktivierung) als Instrument zur Einzelverlaufsbeobachtung bei depressiven Patienten. In: Wolfersdorf M, Straub R, Hole G, editors. *Depressive Kranke in der Psychiatrischen Klinik*. Regensburg: Roderer Verlag, 1984;250-60.
- Rombaut NEI, Hindmarch I. Psychometric aspects of antihistamines: a review. *Hum Psychopharmacol* 1994;9: 157-69.
- Kohnen R, Kyrein HJ, Charissé G. Sedierung bei H_1 -Antihistaminika – eine Metaanalyse (Pilotstudie). Presented on the occasion of the 21st annual meeting of the European Histamine Research Society, Cologne, 1993.
- Lamprecht J, Mösges R, Spaeth J. Treatment of seasonal allergic rhinitis with the new low dose antihistamine antagonist mizolastine. Abstract volume, XIVth International Congress of Allergology and Clinical Immunology, Kyoto (Japan), 1991.
- Bartsch M, Röwer T, Michel O, Spaeth J, Mösges R. Doppelblinde Vergleichsstudie zur Wirksamkeit und Verträglichkeit von Azelastin-Nasenspray in der Monotherapie und in der Kombinationstherapie mit Azelastin-

- Tabletten bei Patienten mit saisonaler allergischer Rhinitis und zusätzlicher Hausstaub/Nahrungsmittelallergie. In: Mösges R, Schlöndorff G, editors. *Topische Therapie der allergischen Rhinitis*. Zülrich: Biermann-Verlag, 1993:153-63.
12. Klimek L, Kurzeja A, Runge HG, et al. Wirksamkeit und Verträglichkeit von Azelastin-Nasenspray im Vergleich mit Cetirizin-Tabletten bei Patienten mit saisonaler allergischer Rhinitis. In: Mösges R, Schlöndorff G, editors. *Topische Therapie der allergischen Rhinitis*. Zülrich: Biermann-Verlag, 1993:138-47.
 13. Korves B, Breuer G, Spaeth J, Mösges R. Bestehen dosisabhängige Wirkungsunterschiede bei der topischen Therapie mit dem H₁-Rezeptor-Antagonisten Azelastin? In: Mösges R, Schlöndorff G, editors. *Topische Therapie der allergischen Rhinitis*. Zülrich: Biermann-Verlag, 1993:164-75.
 14. Mösges R, Klimek L, Spaeth J. ECP-controlled sequential therapy in allergic rhinitis. *Allergo J* 1996; (in press).
 15. Mösges R, Dostal E, Grohmann E, Giani G, Reineke T, Wustrow J. Ist bei der allergischen Rhinitis die Therapie mit Azelastin-Nasenspray wirkungsäquivalent der systemischen Therapie mit Loratadin-Tabletten? In: Mösges R, Schlöndorff G, editors. *Topische Therapie der allergischen Rhinitis*. Zülrich: Biermann-Verlag, 1993:121-9.
 16. Davis RJ, Thomas KE, Ollier S, Ferguson H. The effect of intranasal azelastine, Rhinolast-R, on nasal airway obstruction following provocation testing with histamine and allergen. *Clin Exp Allergy* 1992;22:642-7.
 17. Horak F, Jäger S, Toth J, Berger U, Niruberger E. Azelastine in pollen-induced allergic rhinitis. *Drug Invest* 1994;7(1):34-40.
 18. Baumgarten C, Petzold U, Dokic D, Aurich R, Kunkel G. Modification of allergen-induced symptoms and mediator release by intranasal azelastine. *J Pharmacol Ther* 1994; 2:43-51.
 19. Charpin D, Godard P, Garay RP, Michel FB, Michel HD. Multicentre clinical study of the efficacy and tolerability of azelastine nasal spray in the treatment of seasonal allergic rhinitis – a comparison with oral cetirizine. *Eur Arch Otorhinolaryngol* 1995;252:455-8.
 20. Zander KJ, Beck K, Neues P, Scheidereiter U, Bullinger M. Gesundheitsbezogene Lebensqualität: Methodik und Profil bei der saisonalen und perennialen Rhinokonjunktivitis. *Allergologie* 1993;16:113.
 21. Volkerts ER, van Laar M. Specific review of the psychometric effects of cetirizine. *Allergy* 1995;50 Suppl 24: 55-60.
 22. Zander KJ, Mösges R, Grohmann E, Scheidereiter U, Bullinger M. Zur Lebensqualität allergischer Rhinitiker – ein Vergleich topischer und systemischer Therapie. In: Mösges R, Schlöndorff G, editors. *Topische Therapie der allergischen Rhinitis*. Zülrich: Biermann-Verlag, 1993: 130-7.
 23. Horak F. Seasonal allergic rhinitis – newer treatment approaches. *Drugs* 1993;45(4):518-27.
 24. Schmutzler W. Adverse reactions to H₁-antihistamines. *Allergo J* 1994;8(3):442-50.

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