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Oscillococcinum[R] in patients with influenza-like syndromes:

A placebo-controlled double-blind evaluation

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Abstract

A controlled clinical trial was conducted to assess the effectiveness of Oscillococcinum[R] in the treatment of patients with influenza-like syndromes. 188 patients received the test drug and 184 patients were assigned to the placebo. Data were recorded by the participating physicians at the beginning of the treatment, after 48 hours and after 7–10 days. During the first few days, the patients recorded their rectal temperature twice a day (mornings and evenings), 9 symptoms on a rating scale (cough, catarrh, sore throat, muscle pain, etc.), and use of medication. Recovery was defined as follows: 'rectal temperature < 37.5°C and no headache or muscle pain'. Effectiveness was defined as a statistically significant greater decrease in symptoms after 48 hours in the verum group or a shorter duration of symptoms in comparison to the placebo group. After 48 hours the symptoms of the patients in the verum group were significantly milder ($P = 0.023$) than in the placebo group. The number of patients with no symptoms was significantly higher in the verum group from the second day onwards (verum: 17.4%, placebo: 6.6%) until the end of the patients' recording (day 5 in the evening: verum: 73.7%, placebo: 67.7%). The biggest group difference was recorded for the time between the evening of the second day (10.6% more patients with no symptoms) and the morning of the fourth day (10.2% more patients with no symptoms). The clinical trial showed that treatment of influenza-like syndromes with Oscillococcinum[R] has a positive effect on the decline of symptoms and on the duration of the disease.

KEYWORDS: Influenza-like syndrome; Oscillococcinum[R]; Homoeopathy; Absence of symptoms

Introduction and object of the study

In medicine, influenza-like syndromes are of minor importance since this viral disease disappears within 5–10 days and usually does not result in negative consequences. However, the impaired well-being of the patients makes prophylactic and curative measures necessary. Furthermore, for economic reasons, remedies are needed as one third of absenteeism is due to influenza-like syndromes.

So far more than 200 pathogenic organisms are known to cause these infections of the upper respiratory tract. 5 rhinotrope viral strains are responsible for half of all colds. How the infection is transmitted, either via droplet emission or transfer by hand (e.g. by shaking hands) is not yet known.

However, help might be expected from a homoeopathic preparation which is widely used in France as prophylaxis and therapy to patients suffering from influenza-like syndromes. The drug is Anas Barbariae Hepatis and Cordis Extractum HPUS 200K, commer-

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cialised under the trademark Oscillococcinum[R] (Boiron laboratories).

Despite the widely assumed methodological difficulties in clinical trials of homoeopathic medicines, quite a few studies have been performed.[2–6] The most rigorously designed study on Oscillococcinum[R] was performed by Ferley *et al.*[7]

This study was a placebo-controlled, randomised double-blind evaluation on 478 patients with a mild influenza-like syndrome during an epidemic of the A H1N1 influenza virus. The patients who were treated with Oscillococcinum[R] recovered earlier, this was statistically significant.

Our clinical trial was performed with patients suffering from influenza-like syndromes and was essentially a replication of the study of Ferley *et al.*[7] In addition, there may also be a non-specific effect of the preparation, since it can be assumed that a different virus from that of the Ferley study was responsible for the infection in the present study.

The primary object of the study was to answer the following questions:

1) After 48 hours of treatment with the active drug, has the patient's condition improved more than with the placebo?

2) Were the symptoms eliminated faster in the verum group than in the placebo group?

Data on concomitant medication, compliance and fitness for work were also collected.

Methods

Study design

The trial was a prospective placebo-controlled double-blind multicentric study. Enrolment in the study for 7–10 days was planned for 400 patients, to be recruited from 15–20 medical practices of general practitioners or specialists for internal diseases. The study was conducted in Germany from November 1990 until Spring 1991.

Recruitment of patients

Patients included in the study were selected from those who had consulted a clinician with an influenza-like syndrome. The infection had to have occurred less than 24 hours before entry in the trial. Rectal temperature had to be equal to or above 38°C and the patients had to suffer from muscle pain and headache and at least from one of the following symptoms: shivering, thoracic or periarticular pain, spinal pain, cough, irritation of the nasal mucosa, or a general feeling of illness. Exclusion criteria were: patients under 12 or over 60 years of age; patients who, for preventive reasons, needed to be given an anti-influenzal treatment during the first 48 hours of the study; patients with immune system disorders or local infections and patients who had been immunised against influenza; patients who had been given additional therapy in the form of immunosuppressants or immunostimulants; or those who had taken anti-influenzal medicines, analgesics or antibiotics during the first 48 hours of the trial.

Patients gave written or oral consent before a witness, after having been informed as to the nature, meaning, and extent of the clinical trial.

The patients were randomly allocated to one of the 2 treatment groups, Oscillococcinum[R] or placebo. The randomisation was performed in two steps, verum and placebo were indistinguishable. At Laboratoires Boiron, each placebo and each verum treatment was given a number according to a random list of numbers. Then all the verum and all the placebo treatments were put in two plain boxes, one box being verum and the other placebo. Next Anfomed asked an independent person to prepare a 4 treatment box for each doctor, each containing 2 verum treatments and 2 placebo treatments. These 4 treatment boxes in turn were known by the numbers of the 4 treatments they contained.

Study variables and study period

At the start of the trial, the clinician recorded the patients' age, gender, weight, other diseases or abnormalities, additional medication, rectal temperature and symptoms. After 48 hours, the clinician gave a global impression of the changes in the patients' health and recorded any additional prescriptions. At the end of the trial period (after 7–10 days) the clinician assessed the patients' compliance and recorded adverse events, as well as absence of symptoms and the date of fitness for work. Standardised questionnaires were used.

Twice a day, mornings and evenings, during the first 5 days of treatment the patients had to record in a journal their rectal temperature and medication taken, and to rate 9 symptoms (cough, cold, sore throat, muscle pain, etc.) Target variables were: 1) The overall impression of the clinician concerning changes in the

patients' health after 48 hours, and 2) The date of absence of symptoms. Recovery or absence of symptoms was defined as 'a rectal temperature less than 37.5°C and absence of headache and muscle pain (taken from the patient's daily journals)'.

Other variables were: severity of self-rated symptoms, amount of medication taken, date of return to work and adverse events. The severity of the symptoms of the influenza infection was determined by a total score. This total score had a value between 9 = absence of symptoms (18 = mild, 27 = moderate) and 36 = severe.

Adverse events served as a confidence variable. They were taken from the patients' or the clinicians' records. They gave information on any pathological changes during the time of treatment, whether they were linked to the active drug or not. Additional variables were premature termination of the trial and compliance records.

Medication

The placebo was made of lactose and saccharose. It was presented like the active drug (see introduction) in 3 boxes of 3 doses each, one dose consisted of 200 globules. All patients were asked to take the contents of the tube of medication sublingually, 3 times a day for 3 days.

The first dose was administered at the doctor's office but the following doses were taken by the patients themselves in the morning, at lunch time and in the evening.

Statistical hypotheses and experimental study design

The main object of the trial was to test the effectiveness of Oscillococcinum® in influenzal conditions. Effectiveness was considered attained, if the number of patients in the verum group, who showed no symptoms after the first 48 hours, surpassed the number in the placebo group and/or if the time until elimination of the symptoms was shorter in the verum group than in the placebo group. In keeping with the aim of this study, the following 2 null hypotheses were formulated:

- H(0)1: The number of patients taking the active medicine and showing no symptoms after 48 hours is equal to the number of patients taking placebo and showing no symptoms.
- H(0)2: The duration of disease for the group receiving verum treatment is equal to the duration for the group receiving placebo treatment.

The hypotheses were given a bilateral test in relation to their respective alternate hypotheses: variable 'rates of patients who were affected', and variable 'duration of the disease'. For the null hypotheses having the lowest P value, probability of error was set at alpha = 0.025; for the null hypotheses having the highest P value, probability of error was alpha = 0.05 (Holm procedure).[8] The probability of experimental error was limited to 0.05. In addition to the tests which served to verify the null hypothesis, descriptive tests and tests of inferential statistics were carried out.[9] However, these procedures were only of an exploratory nature and did not serve as a confirmatory testing of the formulated hypotheses.

Homogeneity of the treatment groups was tested with the Fisher exact test and Krauth test.

All patients who were included in the study and received the test drug were included in the analyses for adverse events and compliance. However, for 21 patients from the verum group and 17 from the placebo group, admission and exclusion criteria as defined in the study design were not met. These 38 were not included in the per protocol analyses. Data accuracy was secured by checking the patients' questionnaires on complete and continuous recording.

Findings

Patients

372 patients were enrolled in the study. 188 patients were randomly allocated to the verum group, 184 to the placebo group.

Table 1 shows the distribution on factors of age, gender etc.

The arithmetic mean for severity of symptoms at the start of the treatment, measured with the total score, showed moderate symptoms.

At the start of the study, the average temperature of the patients in the Oscillococcinum® group was 38.8°C, in the placebo group 38.7°C. 15 patients in the verum group and 12 in the placebo group suffered from additional disease.

Out of 188 patients in the verum group 86.2% were without concomitant medication at the start of the study and during the first day of treatment. In the placebo group 91.3% out of

Feature	Verum group			Placebo group		
	n	m	sd	n	m	sd
Patients	188			184		
female	93			88		
male	95			96		
age		35.1	12.7		34.9	12.1
Broca index at the start of the study		1.1	0.2		1.1	0.2
body temperature (°C)		38.8	0.4		38.7	0.5
severity of symptoms (total score)		24.7	5.4		24.7	5.1
Other additional studies						
absolute	15			12		
percent	8.0			6.5		

TABLE 1. Statistical description of the patients.

	no influenzal symptoms		clear improvement		improvement		no improvement		worse	
sample	n	%	n	%	n	%	n	%	n	%
verum	32	19.2	73	43.7	41	24.6	21	12.6	0	0.0
placebo	25	15.0	56	33.5	49	29.3	28	16.8	9	5.4
total	57	17.1	129	38.6	90	27.0	49	14.7	9	2.7

TABLE 2. Symptoms after 48 hours.

184 patients were without additional medication during this period (Table 1).

Treatment efficacy

In the course of the trial period, 21 patients in the verum group and 17 in the placebo group violated the protocol, for instance, by insufficient compliance. These patients were not considered in the following analyses of effectiveness: situation after 48 hours, date of absence of symptoms and final assessment.

In the following description, the reduced sample of 334 patients comprises 167 in the verum group and 167 in the placebo group.

Comparison after 48 hours

After 48 hours, the change in the patients' condition was assessed. At this time point 19.2% of the verum group had no symptoms and 43.7% had clearly improved (see Table 2, Figure 1). In the placebo group, the patients' condition had improved less. According to the Krauth test, the null hypothesis (the number of patients free of symptoms after 48 hours is equal in both treatment groups) was contradicted at a statistically significant level. The data show a clear improvement in health in the verum group.

Probability by the Krauth test: $P = 0.0028$.

Date of absence of symptoms

The second question concerned the date of elimination of the symptoms. The statistical analysis was based on the mean date of elimination of symptoms. The proportions of patients with no symptoms were compared after 48 hours. The distribution is given in Figure 2. On the morning of the second day, 9.6% of the verum group and 1.8% of the placebo group had no symptoms. On the second day, in the evening 17.4% of the verum group and 6.6% of the placebo group were free of symptoms. After 5-day recording of body temperature and influenzal symptoms, 26.4% of the verum patients and 32.3% of the

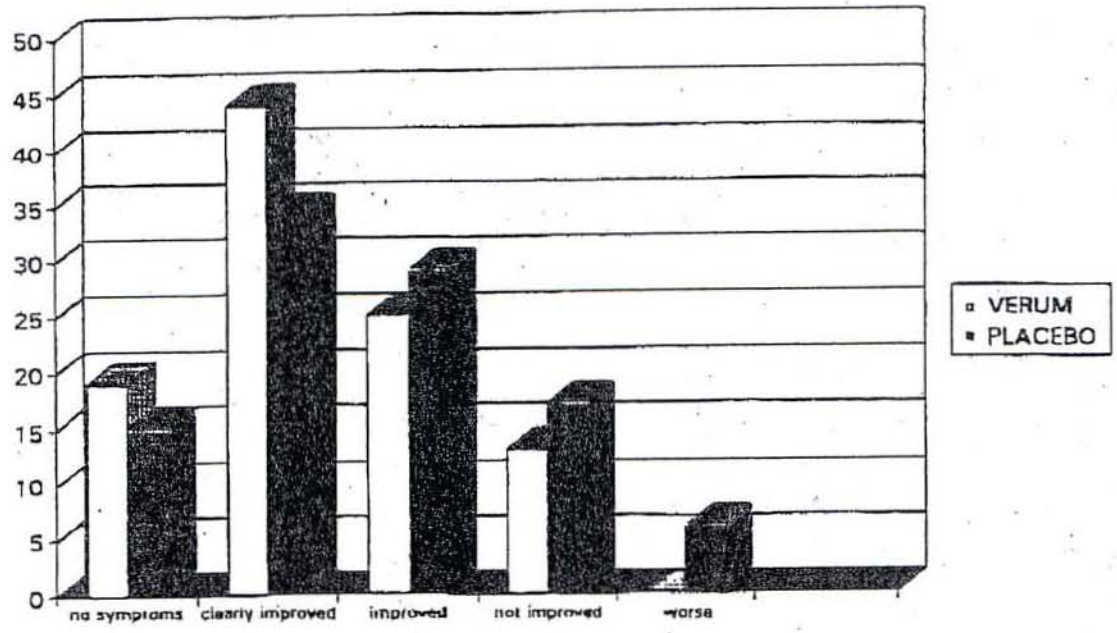

FIGURE 1. Findings after 48 hours.

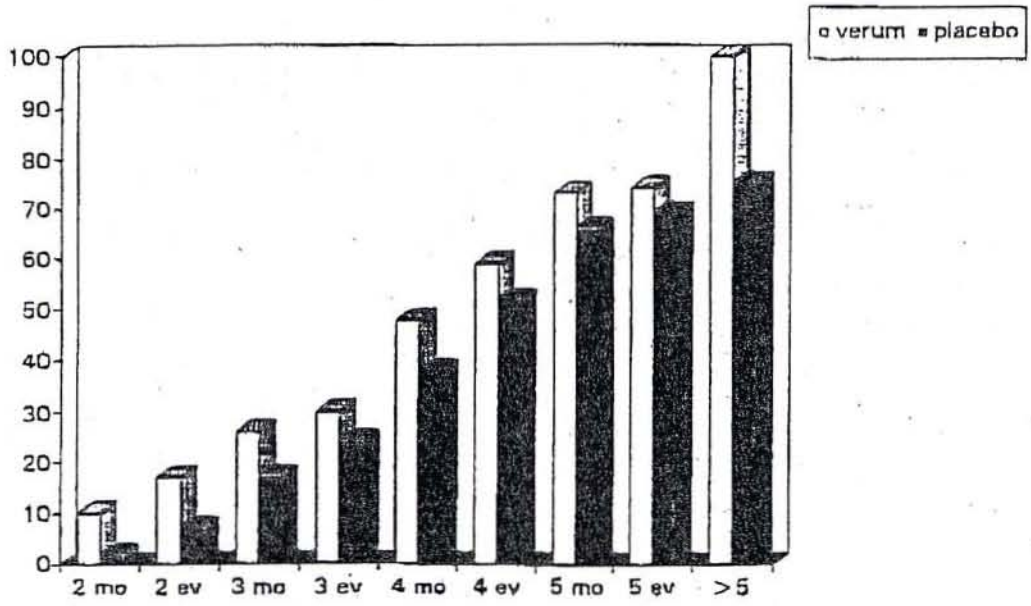

FIGURE 2. Absence of symptoms.

placebo patients had not yet eliminated all their symptoms. The difference in the treatment groups concerning the date of elimination of the symptoms was statistically significant.

Probability by the Krauth test: $P = 0.023$.

Other variables

For further information on the effectiveness of the preparation, the following were investigated: severity curve of the symptoms, body temperature, amount of medication taken and date of fitness for work. The improvement scores are given by categories (clearly improved, improved ...) which were defined in the protocol and results presented (Table 2).

Severity of symptoms and body temperature

The total score taken from the patient's journal gives the severity of symptoms. In the verum group, the values are lower from the first evening compared to the placebo group.

The curve of the decline in individual symptoms runs parallel to the general trend[9] as can be seen in Figure 3 which gives a picture of the

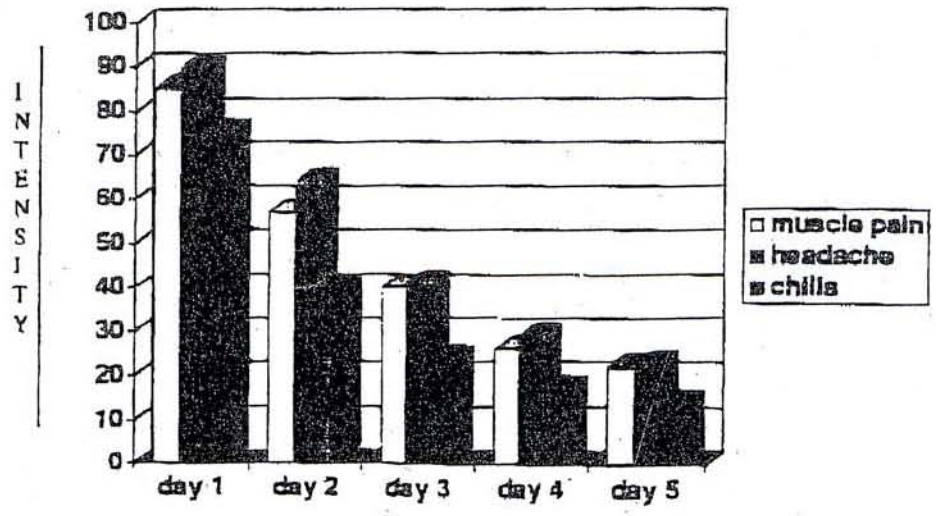

FIGURE 3A1. Evening symptoms/verum.

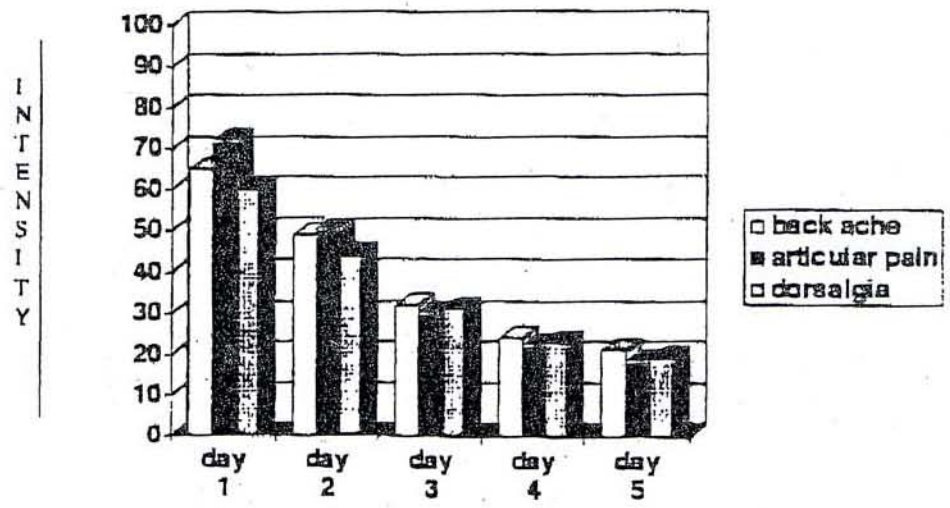

FIGURE 3A2. Evening symptoms/verum.

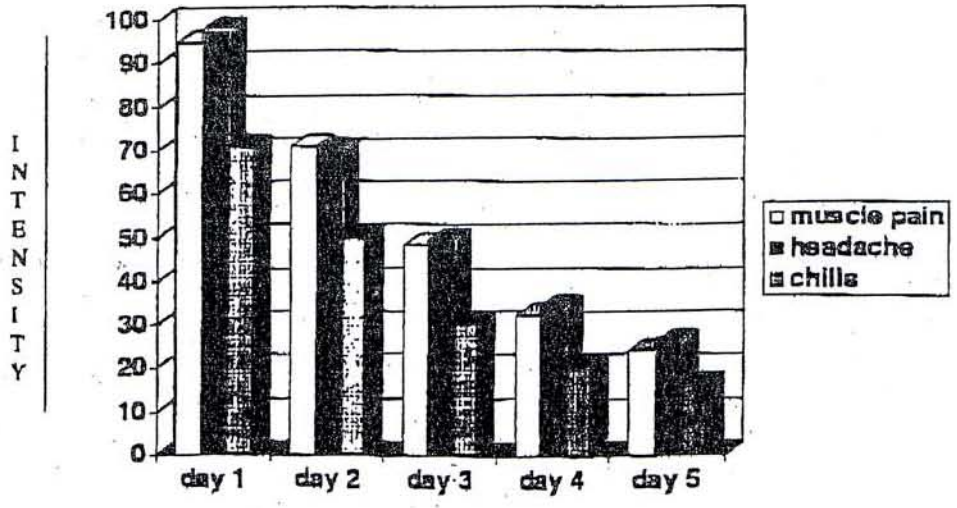

FIGURE 3B1. Evening symptoms/placebo.

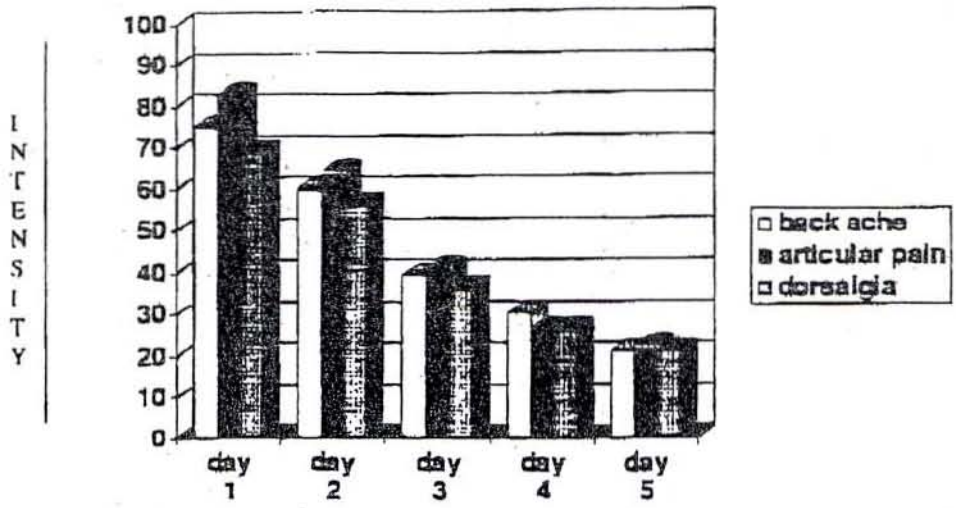

FIGURE 3B2. Evening symptoms/placebo.

severity of symptoms in the evening, in both treatment groups.

From the first morning of the trial until the fourth evening, the mean values of the body temperature were lower in the verum group than in the placebo treatment group. However, these additional variables do not provide any new information since they were partially included in the target variables.

Concomitant medication

After the first 48 hours, some of the patients in both groups received concomitant medication. Analgesics and anti-rheumatics were the most frequent, followed by cough medicine and expectorants. Anti-influenzal medication as concomitant therapy played a minor role in both groups.[9] The frequency of additional medication use was higher in the placebo group than in the verum group. Over the course of the trial the number of patients who received concomitant medication clearly increased in both groups: in the verum group it increased from 13.8% to 30.3% and in the placebo group from 8.7% to 36.4%. This difference between the treatment groups continued with the percentage of patients in need of 2 or even 3 concomitant medications: in the verum group 11.7% of the patients took 2 additional medicines and 2.1% used 3 medications. In the placebo 16.3% of the patients took 2 additional medicines and 3.3% took 3 different preparations.

Fitness for work

In the verum group the percentage of patients fit for work was slightly higher throughout the trial than in the placebo group. After 2 days, the percentage was 16.3% in the verum and 9.3% in the placebo group. After 4 days, 48.9% of the patients in the verum group and 46.7% in the placebo group felt fit for work.

Final assessment of effectiveness

7–10 days after the start of the trial the general practitioners made a final assessment of the patients' health. They found that 133 (80.1%) of the verum patients had no symptoms. In the placebo group 128 (77.1%) had recovered. 2 patients had not continued their daily journals. The differences between the treatment groups was not statistically significant ($P = 0.5073$).

Premature termination of the study and adverse events

95.7% of the verum patients and 89.1% of the placebo patients finished the entire study. In both groups the main reason for a premature end to the trial was insufficient medication compliance.

This was true for 2.7% of the patients in the verum group and 8.2% in the placebo group. 5 patients reported adverse events. However, according to the opinion of the physicians in 4 of the 5 cases, the adverse events were not connected with the medication. Only one patient suffered from headache which might have been caused by the medication.

Discussion

This clinical trial in outpatient care was designed to investigate whether the successful treatment of influenza-like syndromes with Oscillococcinum® reported by Ferley *et al*[7] could be repeated.

With regard to the main points in question, the study findings were quite coherent with Ferley's findings:

1) The decline in symptoms after 48 hours of treatment with the active drug was significantly higher in the verum group than in the placebo group.

2) Symptoms disappeared significantly faster in the verum group than in the placebo group.

The results based on the patients' journals recording: influenzal symptoms, concomitant medication, fitness for work and compliance in the verum group, all supported the effectiveness of Oscillococcinum[R] in influenza-like syndromes. Side effects were apparently of no consequence. However, not all of the verum patients could be treated effectively with Oscillococcinum[R]. The health of 12.6% of the patients of the verum group (16.8% of the placebo group) had not improved after 48 hours. Almost one third of the patients in the verum group took additional medication during the trial. The fact that according to final assessment, 80% of the patients of the verum group (77% of the placebo group) had recovered is not surprising since the disease lasts only 5–10 days even without medication.

Oscillococcinum[R] either has a modest curative effect or, perhaps, it is more effective with specific pathogens. Rather, it can be assumed that Oscillococcinum[R] has a non-specific effectiveness, since in the present study it showed a stronger effect after 48 hours (about 11% of the patients were without symptoms after 2 days) than in the Ferley (7%) study, which probably investigated a different influenzal virus. Therefore, the statement of Ferley *et al*[7] can be confirmed: 'The effect was modest..., but nevertheless is of interest'. The positive effects of a treatment with Oscillococcinum[R] were more apparent when gradual changes were considered. 62.9% of the patients had clearly improved in their health condition after 48 hours and only 12.6% had not improved. In the placebo group 48.3% patients had clearly improved and 22.1% showed no improvement.

This clinical trial confirms the curative effect of Oscillococcinum[R]. However, to investigate prophylactic effectiveness, additional studies must be carried out. But future studies might be of great interest from the viewpoint of personal well-being, as well as from administrative and economic points of view.

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