Original research and audit

OscillococcinumR 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 OscillococcinumR 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 OscillococcinumR has a positive effect on the decline of symptoms and on the duration of the disease.

KEYWORDS: Influenza-like syndrome, OscillococcinumR, Homeopathy, 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 homeopathic preparation which is widely used in France as prophylaxis and therapy to patients suffering from influenza-like syndromes. The drug is Anas Biarbaiae Hepatis and Cordis Extractum HPUS 200K, commer-

U. Wehmann J. van der Zee H. where angels fear to tread. Homo-97, 10: 76–78.

TED CHAPMAN

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cialised under the trademark Oscillococcinum® (Boiron laboratories).

Despite the widely assumed methodological difficulties in clinical trials of homoeopathic medicines, quite a few studies have been performed. The rigorously designed study on Oscillococcinum® was performed by Ferley et al. This 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® 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. 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 illness 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-influenza 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-influenza medicines, analgesics or antibiotics during the first 48 hours of the trial.

Patients gave written or oral consent before being included. 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® or placebo. The randomisation was performed in two steps, verum and placebo were indistinguishable. At Laboratoire 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 the organism asked an independent person to prepare a 4 treatment box for each doctor, each containing 2 verum treatments and two 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 report 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) absence of symptoms. Recovery of symptoms was defined as 'a reduction of 37.5°C and absence of muscle pain (taken from the patient's journal)'. Other variables were: severity of symptoms, amount of medication, return to work and adverse events.

Adverse events served as a control. They were taken from the patients' doctors' records. They gave an insight into any pathological changes during treatment, whether they were by active drug or not. Additional variables were premature termination of the trial, adverse events.

Medication

The placebo was made of lactose. It was presented like the active drug. In introduction) in 3 boxes of 3 doses: 900 mg of 3 globules were asked to take the contents of medication sublingually, 3 times a day.

The first dose was administrated at the doctor's office on the day following the patients' self-recording, at lunch time and in the evening.

Statistical hypotheses and experimental design

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

H0(1): The number of patients taking active medicine and showing no symptoms after 48 hours is equal to the number of patients taking placebo and with symptoms.

H0(2): The number of patients taking active medicine and showing no symptoms after 48 hours is equal to the number of patients taking placebo and with symptoms.

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the nasal mucosa, or a
ness. Exclusion criteria
12 or over 60 years of
for preventive reasons,
anti-influenzal treatment
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disorders or local infec-
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ents who had been given
3) the form of immuno-
nunostimulants; or those
antibiotics, medicines,
toxic during the first 48

in or oral consent before a
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be performed in 15. Placebo
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patients' health after 48 hours, and 2) The date
of absence of symptoms. Recovery or absence
of symptoms was defined as 'a rectal tempera-
ture 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 vari-
able. They were taken from the patients' or the
clinicians' records. They gave information on
any pathological changes during the time of
reatment, whether they were linked to the
active drug or not. Additional variables were
premature termination of the trial and compli-
ance records.

Medication
The placebo was made of lactose and sacchar-
ose. 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
docor's home but the following doses were
aken by the patients themselves in the morn-
ing, 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 Osellilococcus in influen-
zial 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): 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(02): 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 hypo-
theses: 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). The prob-
ability 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
inference statistics were carried out. 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 Kruskal

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 2 patients from the verum
group and 17 from the placebo group, admi-
sion and exclusion criteria as defined in the
study design were not met. These 19 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 I shows the distribution on factors of
age, gender etc.
The arithmetic mean for severity of symp-
toms at the start of the treatment, measured with
the total score, showed moderate symptoms.
At the start of the study, the average tempera-
ture of the patients in the Osellilococcus
...
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 Krath 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 Krath test: \( P = 0.0023 \).

**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 6.6% 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 influenza symptoms, 26.4% of the verum patients and 32.3% of the placebo patients had not yet eliminated symptoms. The difference in groups concerning the date of elimination of the symptoms was statistically significant.

Probability by the Krath test.

**Other variables**

For further information on the exclusion criteria, the preparation, the following variables were recorded: severity curve of the symptom, amount of medication, date of fitness for work. The
Placebo group

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**FIGURE 1. Findings after 48 hours.**

The null hypothesis (the number of no symptoms after 48 hours is statistically significant) was not rejected. The improvement in health in the study groups was significant by the Krath test: $P = 0.0028$.

The question concerned the date of onset of symptoms. The statistical analysis was based on the mean date of average onset. The proportion of no symptoms among the treated patients was compared. The distribution is given in Table 1.

On the morning of the second day, the verum group and 1.8% of the placebo group had no symptoms. On the afternoon, in the evening 17.4% of the verum group and 6.6% of the placebo group had no symptoms. After 5-day recording of temperature and influencing symptoms, the verum patients and 32.3% of the placebo patients had not yet eliminated all their symptoms. The difference in the treatment groups concerning the date of elimination of symptoms was statistically significant.

**FIGURE 2. Absence of symptoms.**


**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 as can be seen in Figure 3 which gives a picture of the...
severity of symptoms in the evening.

From the first morning of the trial, to the fourth evening, the mean values of the temperature were lower in the verum group than in the placebo treatment group. These additional variables do not provide new information since they were not 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-inflammatories were frequent, followed by cough medicine and expectorants. Anti-influenza medication was also frequently used. Concomitant therapy played a role in both groups. The frequency of additional treatment was higher in the placebo group compared to the verum group. Over the course of the trial, the number of patients receiving additional medication clearly increased in both groups. In the verum group it increased from 30.2% to 36.4%, while in the placebo group it increased from 36.4% to 41.7%. This difference between the groups continued with the percentage in need of two or more concomitant medications. In the verum group 11.7% of the patients received additional medicines and 2.1% used additional medications. In the placebo group 16.3% of the patients received additional medicines and 5.3% used additional preparations.

Fitness for work
In the verum group the percentage of patients able to work was slightly higher than in the placebo group. After
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. 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 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: influenza symptoms, concomitant medication, fitness for work and compliance in the verum group, all supported the effectiveness of Oscillococcinum in influenza-like syndromes. Side effects were apparently of no consequence. However, not all of the verum patients could be treated effectively with Oscillococcinum. The health of 12.6% of the patients in 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 in 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 either has a modest curative effect or, perhaps, it is more effective with specific pathogens. Rather, it can be assumed that Oscillococcinum 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 influenza virus. Therefore, the statement of Ferley et al. can be confirmed: ‘the effect was modest, but nevertheless of interest’. The positive effects of a treatment with Oscillococcinum 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 trial confirms the curative effect of Oscillococcinum. 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.

References

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A retrospective study on homeopathic medical
MICHIEL VAN WASSENHOV

Introduction
To date, thousands of individual descriptions have been published by homeopathic physicians. Most spectacular cures, since with in it is essential to show someth that is remarkable to justify publication, true that individual case studies ture an evaluation of the efficacy of homeopathy in daily practice.

Open or blind prospective trials allow such an evaluation with definitive rigour; however, the need for placebo-controlled treatment of each case—except for correct practice of homeopathy is generally difficult for this type of study.

The first step necessary to improve homeopathic practice in prospective trials. Only such trials allow us to evaluate the effects used in future prospective studies, and to also evaluate the who would wish to take part.

Having 23 years experience in homeopathy, 17 in homeopathy, and 18 years of computerisation of my personal case book (3,673 records), it seemed useful to type of work, especially in view of the experience gained by my public arthritis. The experience of impr...