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A controlled evaluation of a homoeopathic preparation in the treatment of influenza-like syndromes

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1 A controlled clinical trial was conducted to assess the effectiveness of a homoeopathic preparation in the treatment of influenza-like syndromes.
2 237 cases received the test drug and 241 were assigned to placebo. Patients recorded their rectal temperature twice a day, and the presence or absence of five cardinal symptoms (headache, stiffness, lumbar and articular pain, shivers) along with cough, coryza and fatigue.
3 Recovery was defined as a rectal temperature less than 37.5° C and complete resolution of the five cardinal symptoms.
4 The proportion of cases who recovered within 48 h of treatment was greater among the active drug group than among the placebo group (17.1% against 10.3%, $P = 0.03$).
5 The result cannot be explained given our present state of knowledge, but it calls for further rigorously designed clinical studies.

Keywords homoeopathy influenza clinical trial

Introduction

Few clinical trials have been performed to evaluate homoeopathic therapy (Aulas, 1985; Reilly *et al.*, 1986). This situation is largely due to the rationale of homoeopathic prescription by which the precise nature of the treatment is adapted to the specific symptoms of a patient suffering from a given disease. The treatment is based on the 'simillimum' principle, using infinitesimal concentrations of drugs which have the ability to induce, in healthy individuals, symptoms similar to those presented by sick persons. Although a regular feature of homoeopathic treatment is that two patients who have the same disease are liable not to benefit from the same treatment, a school of thought soon developed (Finella, 1877) that certain diseases, especially some acute diseases, could be treated with substances or drug mixtures tailored to the disease characteristics alone.

Homoeopathic physicians are far from reaching agreement about such drugs, which would be prescribed without taking account of the particular symptoms of each patient. Nevertheless, these drugs are gaining popularity among large sections of the medical profession and among the public who buy them over-the-counter.

These preparations provide the opportunity to design conventional trials in a way that has not so far been possible with regular 'unitarian' drugs.

The following experiment deals with a drug of the former category. Its action on the treatment of influenza and influenza-like syndromes was evaluated. It is a homoeopathic preparation currently on the market, made of a highly diluted autolysate of animal organs.

Methods

Study design

The trial was implemented with the participation of general practitioners of the Rhône-Alpes region in France (regional capital: Lyon). Most of them were not homoeopathic clinicians. Patients included in the study were chosen from

those who attended with influenza-like syndromes and who agreed to participate in the experiment after a formal briefing. The treatment allocation of active drug or placebo was made on a randomized double-blind basis. For the final evaluation a second visit to the physician's practice was planned for a week later.

Admission criteria

To be eligible patients had to be 12 years old and over, to suffer from an influenza-like syndrome defined by the association of a rectal temperature equal to or above 38° C, and at least two of the following symptoms: headache, stiffness, lumbar and articular pain, shivers. The first manifestation had to have occurred less than 24 h before entry.

Patients with immune deficiency or local infection were not included. Also excluded were those who had had immunization against influenza or who were under treatment either for depression or for stimulation of immunity.

Patients were asked not to take any drug for pain or fever during the 48 h following entry or, if they should do so, to record this use along with any use of antibiotics.

Study period

The definition of influenza-like syndrome was entirely clinical, and it was decided to undertake the experiment during an influenza epidemic. Two sources of information on the occurrence of such an epidemic were used. One was the national computer network set up by the 'Institut National de la Santé et de la Recherche Médicale' (Research on Biomathematics and Biostatistics Unit) and the 'Direction Générale de la Santé' of the Health Ministry (Valleron *et al.*, 1986; Direction Générale de la Santé, 1987b). This network then included about 300 sentinel practices scattered across the country (of which 23 were in the study region). It allows the weekly surveillance of the incidence of influenza-like syndromes at a national and regional level. It also publishes the results of identification tests on respiratory viruses made through the two National Reference Laboratories (South and North of France).

The second information source was a local network of 12 sentinel practices monitored for the purpose of the study (Figure 1).

The A H1N1 influenza virus was isolated in the study region 7 days after the study managers issued the instruction to start including patients in the experiment. Enrolment continued after the epidemic period, but 71% of all cases were entered during the peak of the epidemic. The study managers decided to include no further patients when it became apparent that the epidemic had ended. The main concern was to restrict the trial to those cases that were most likely to be cases of influenza.

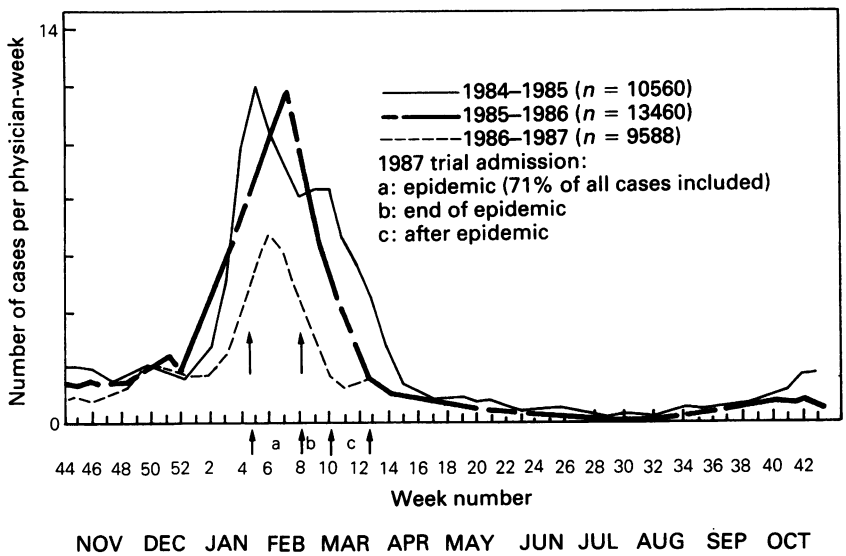

Figure 1 Influenza-like syndromes notified by the sentinel physicians between 1984 and 1987 through the National Computer Network on transmitted diseases; national data and trial admission period (Source: Direction Générale de la Santé, 1987b).

The homoeopathic preparation

The drug is commercialized under the trademark Oscillococcinum® by Boiron Laboratories. It is made of *Anas Barbariae Hepatis* and *Cordis Extractum* HPUS 200 C.

It is presented as granules (200 granules per dose). The vehicle is made of lactose and saccharose. The placebo, whose presentation was identical, was made of lactose and saccharose alone.

The standard treatment dispensed is one box containing five doses. The first dose was administered sublingually at the medical practice; the remaining four were taken on the following mornings and evenings. The doses were dispensed with a code number which was identified only after analysis of the data. Allocation of the active drug and placebo was balanced in every eight boxes. Each physician had to enrol between four and six patients.

Study diaries and monitoring

For 1 week patients noted morning and evening their temperature and the presence or absence of the five cardinal symptoms. Cough, coryza and fatigue were also recorded along with any use of medications or any side effects. Finally they were asked to make their own record of how effective they found the treatment to be.

Evaluation criteria

Recovery was defined as a rectal temperature less than 37.5° C and complete resolution of the five cardinal symptoms. Persistence of cough, coryza or fatigue was accepted. The main evaluation criteria set prior to data analysis were the recovery rate within 48 h of treatment (i.e. proportion of patients who had recovered within 48 h), and the time trend of this rate, as this gives insight into the consistency of the observed effect. Additional criteria were also examined e.g. the patients' judgement on the effectiveness of the treatment and whether any additional drug was taken.

Statistical analysis

Comparison of percentages were performed using Pearson's χ^2. Adjustment for some identified or potential confounders was done by a Mantel-Haenszel procedure (Mantel, 1963) or by a multivariate logistic regression analysis. Crude data analysis was performed with a hand calculator using Rothman's programs (Rothman & Boice, 1984). Confidence interval estimation followed Miettinen's method (1976). The time trend analysis of the recovery rate (actuarial method) was performed with a logrank test (Mantel, 1966), if necessary adjusted for some cofactors (Dash package from the Dana Farber Institute, Harvard University, Boston, run on VAX-VMS).

Results

Comparability of the two groups and general features of illness

Of 487 cases entered 478 met the admission criteria. Table 1 shows that the two groups were reasonably similar. Nine cases were not included in the analysis because they were not eligible (temperature lower than 38° C, delay before entry of greater than 24 h, or the presence of less than two cardinal symptoms). Five had been assigned to the active drug group and four to the placebo group.

43% of the cases had fairly severe illnesses at the initial visit, with temperature ≥39° C and the presence of at least three out of the five

Table 1 Initial comparison between treatment groups

	Active drug	*Placebo*
Number eligible cases	237	241
Sex-ratio M/F	93/127 (0.73)	97/129 (0.75)
Age* (years)	33.7 (1.7)	35.1 (1.9)
Inclusion during the epidemic peak (%)	73.6	69.2
Delay*** < 12 h (%)	48.2	52.0
Temperature at inclusion* (°C)	38.9 (0.07)	38.8 (0.07)
Severe illnesses (%)**	43.8	42.1

* mean (mean deviate)

** at least three of the cardinal symptoms present and temperature ≥ 39° C

*** delay before inclusion

Table 2 Recovery rate within 48 h of treatment

	Active drug n = *228*	*Placebo* n = *234*
Recovered *n*	39	24
%	17.1	10.3

$\chi^2_1 = 4.60$; $P = 0.03$

cardinal symptoms. If the whole observation period is considered, 58% of the patients had all five cardinal symptoms.

The most common symptoms at inclusion were fever (100% greater than 38° C), fatigue (95%), muscle pain (92%), shivers (91%), and headache (89%). Three other symptoms were less frequent: lumbar pain (70%), coryza (59%), and cough (58%). The last two symptoms often occurred secondarily and were found at some time during the week of observation among 84% and 81% of cases.

Recovery rate within 48 h

Recovery rate within 48 h of treatment was greater in the group which received the active drug than in the placebo group (Table 2). The relative efficacy of the drug can be estimated by the ratio of the recovery rates in the two groups. This relative risk (RR) of recovery was 1.67 (95% CI 1.1–2.7, $P = 0.03$). The 'attributable fraction', which is the difference in the proportions of cases who recovered within 48 h, was 6.8% (95% CI 0.6–13%). The proportion of recoveries related to the active drug was greatest 36 h after treatment at 39.6% (95 CI 4–62%).

Some parameters which were potential confounders of the association between the drug effect and recovery were included as covariates in a multivariate logistic regression model, as binary variables: age (< 30 years; ⩾ 30), period of entry (during the epidemic, after the epidemic), delay before treatment administration (< 12 h or 12–24 h after onset of symptoms), severity of the syndrome (moderate: < 39° C, two symptoms; intense: ⩾ 39° C, three + symptoms), use of symptomatic drugs (against fever, pain, inflammation, cough or coryza) during the first 48 h (yes, no), antibiotic therapy (yes, no). Controlling for these covariates did not alter substantially the effect of the drug, which remained significant (OR = 1.9, 95% CI 1.1–3.4; $P = 0.02$). (In this setting, the Odds-Ratio (OR) is a reasonably good approximation of the relative risk). Interaction terms were tested and dropped from the model. In addition to the drug two other parameters showed significant association with recovery, namely age and severity of the syndrome at admission. Tables 3 and 4 give insight into these effects, showing that drug efficacy seems greater among younger patients (67.6% of recoveries within 48 h were related to

Table 3 Recovery within 48 h according to age and treatment group

Age (years)	*Recovery*	*Active drug*	*Placebo*	*Efficacy (RR* and* P *value)*
12–29	Yes	21 (25.0%)	6 (8.1%)	3.1
	No	63	68	$P < 0.01$
30 +	Yes	13 (10.6%)	11 (8.4%)	1.3
	No	110	120	$P = 0.56$

Mantel-Haenszel $\chi^2_1 = 5.82$; $P = 0.01$; $RR_{MH} = 2.06\ [1.1 - 3.4]$ Heterogeneity $\chi^2_1 = 2.46$; $P = 0.12$

Table 4 Recovery within 48 h, according to severity of syndrome and treatment group

Severity of syndrome*	*Recovery*	*Active drug*	*Placebo*	*Efficacy (RR and P value)*
Severe	Yes	7 (7.1%)	8 (8.2%)	0.9
	No	91	90	$P = 0.80$
Mild to moderate	Yes	31 (24.6%)	16 (11.9%)	2.1
	No	95	119	$P < 0.01$

Mantel-Haenszel $\chi^2_1 = 4.64$, $P = 0.02$; $RR_{MH} = 1.72\ [1.1 - 2.8]$; Heterogeneity $\chi^2_1 = 2.29$; $P = 0.13$

* See definition in text.

the drug [95% CI 29–85%]), and when the syndrome was mild or moderate (the proportion of recovery related to the active drug was then 51.6% [95% CI 20–70%]).

Time trend of the recovery rate

Figure 2 (upper part) illustrates the actuarial analysis of the recovery trend between the treatment groups. A log-rank test with stratification on age confirmed the preceding result, showing nearly-significant efficacy of the drug over the whole 1 week observation period (RR = 1.2 [95% CI 1.0–1.4], $P = 0.07$). Most cases recovered before the end of the week after entry. It is no surprise, therefore, that the recovery curves get closer by the end of the observation period, thus lessening the difference between the two treatment groups.

Complementary evaluation criteria

More patients in the placebo group did use adjuvant drugs for pain or fever (50.2% against 40.7%, $P = 0.04$) during the first 48 h. Other symptomatic drugs against cough or coryza were equally used in both groups (39.4% among placebo cases against 37.7%; the same held true for antibiotics (8.6% and 7.6%). It was not possible to compare the amount of analgesic and antipyretic drugs used in each group.

Finally, the number of patients who made favourable judgements on the efficacy of the treatment was greater among the active drug group (61.2% against 49.3%; $P = 0.02$).

Discussion

Patients with an influenza-like syndrome who received the homoeopathic preparation showed

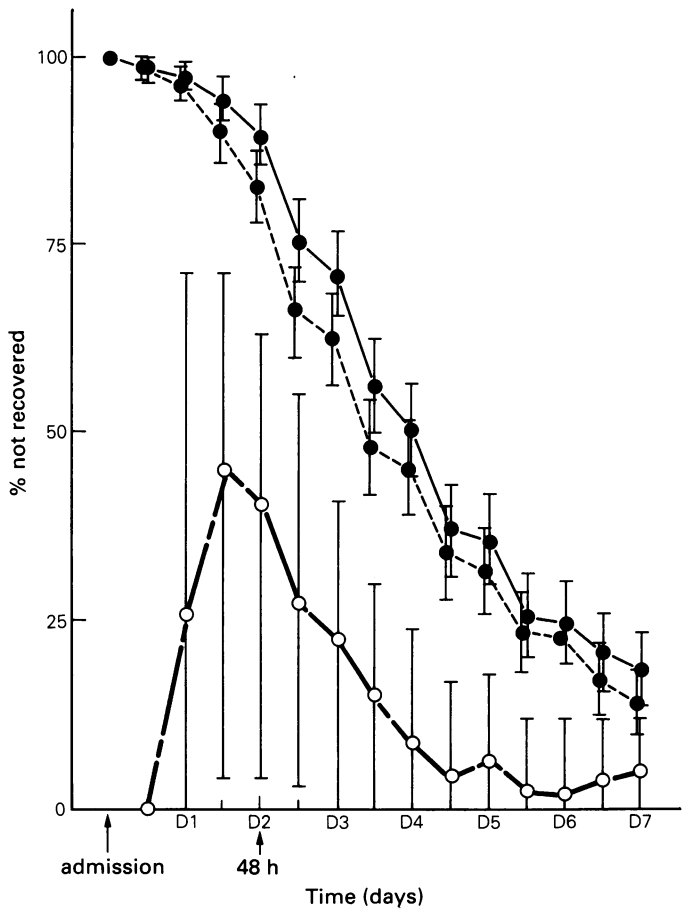

Figure 2 Actuarial recovery curve according to the treatment group (95% confidence interval) and proportion of recoveries related to the active drug (95% confidence interval). ●——● placebo group, ●---● active drug group, ○—-○ % recoveries related to the active drug.

a greater early recovery rate than those who received placebo. This study sheds no light on the mode of action of this drug. Despite the use of terms such as 'attributable fraction' which have specific meaning in clinical epidemiology parlance, it would be unwise to claim that the study has demonstrated a cause and effect relationship between the drug and the recoveries. The positive effect of the homoeopathic preparation cannot be explained in our present state of knowledge, and thus calls for further investigation. The effect was modest (the increase in proportion of recoveries within 48 h was less than 7%), but nevertheless is of interest.

The patients were the main source of information in that they themselves recorded the clinical data twice a day. It might be suggested that physicians would have been more reliable observers. However due to the relative mildness of the disease studied, such an experiment could not be conducted in an institutional setting. Therefore, monitoring by physicians would have been incomplete and lacking in continuity. One consequence of this self-surveillance system is that the response rate might have been poor for some items. The proportion of unanswered questions was lower than 4.8% for the key questions which were used to assess recovery, but did reach 12% for some items of secondary importance. However, missing data were balanced between the two groups.

Another weakness stems from the choice of criteria for the influenza-like syndrome. The definition was purely clinical and probably lacked specificity. However the clinical picture was quite complete, with 58% of cases having all five symptom criteria during their illness, in addition to fever, and 81% having at least four of them. Moreover almost three out of four cases occurred during the peak of the influenza epidemic of the 1986–1987 winter. The conclusions do not differ whether the cases were collected during the epidemic period or afterwards, as demonstrated by the multivariate analysis.

The influenza virus A H1N1 was identified during this epidemic, which was of mild intensity. It was a variant of a strain that appeared in 1977 and which was analogous to an epidemic agent encountered between 1947 and 1957 (Direction Générale de la Santé, 1987a). Hence this virus mostly spread among people born after 1957 (i.e. less than 30 years old) (Hannoun & Lhillier, 1987). In consequence it is possible that many older patients included in the study suffered from syndromes that were caused by other viruses than the influenza virus. Respiratory syncitial virus was very active during the 1986–1987 winter in France (Hannoun & Lhillier, 1987). The partitioning of the data set into 'old' and 'young' cases, with 30 years as the threshold, was decided during the data analysis with the aim of testing age effect in reasonably similar sample sizes. It was not conditioned by any prior hypothesis as to the immune status of older patients. However as the drug was more effective among patients aged less than 30 years, one might speculate that the action of Oscillococcinum® was more specifically active against the influenza virus. Clearly further studies are required to examine this possibility.

One earlier study was conducted with a small sample size and with a rather wide definition of influenza infection (Gassinger *et al.*, 1981). It showed no evidence of an effect of a homoeopathic substance as compared with acetylsalicylic acid. Another trial used a definition of influenza-like syndrome which was similar to the present study but did not reveal any preventive effect of a homoeopathic complex (Ferley *et al.*, 1987). Our study did not aim to evaluate the homoeopathic approach as a whole, but to test a specific preparation.

While pharmacological studies have been published recently (Cazin *et al.*, 1987; Davenas *et al.*, 1987, 1988), conventional clinical trials published in the non-homoeopathic literature are exceptional (Reilly *et al.*, 1986). Reviews (Aulas *et al.*, 1985: Scofield, 1984) stress the weakness of most homoeopathy trials and underline the methodological difficulties of such an enterprise. This tends to enhance the suspicion of those who are detractors of this therapeutic approach. Although it may be enjoying a revival among sections of the population at large and among part of the medical profession, only rigorous clinical experiments will allow vindication of this approach.

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