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Test of a Homeopathic Dilution of Aconitum napellus

A Clinical, Randomized, Double-Blind, Controlled Crossover Study in Healthy Volunteers

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Key Words
Homeopathic potencies · Aconitum napellus · Randomized trial · Crossover study · Placebo · Humans

Schlüsselwörter
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Summary
Background: Although healthy persons often report on reactions to homeopathically diluted substances, the mechanism behind such reactions remains unclear. This study examines whether a distinction can be made between the short-term reactions of healthy volunteers to a homeopathically diluted substance – Aconitum napellus C30 – and to a placebo. **Participants and Methods**: From the 33 subjects randomized for this double-blind, placebo-controlled crossover study, 27 could be included in the analysis. The study comprised two 7-day-long treatment periods, each including the intake of a study preparation for 3 days and a wash-out period of 4 days. One group was first treated with Aconitum napellus C30 and then with placebo; the other group received the two study preparations in the reverse order. The signs and symptoms before the first treatment and after each treatment were collected, evaluated, weighted and repertorized. Based on this classification the blinded physician assessed these signs and symptoms as study outcome parameter to represent the responses to each of the study preparations. Statistical analysis of the data was performed using the Wilcoxon-Mann-Whitney rank test. **Results**: Crossover differences yielded statistical significance between the classified reactions towards Aconitum napellus C30 and to placebo ($p = 0.004$). **Conclusions**: A clear difference between the reported short-term reactions of healthy subjects towards Aconitum napellus C30 and towards placebo was shown. The crossover design with intra-individual comparisons proved to be adequate to recognize the study preparations and for the statistical analysis of a small population sample.

Zusammenfassung
Hintergrund: Reaktionen von gesunden Menschen auf homöopathische Mittel werden zwar häufig berichtet, der diesen Reaktionen zugrundeliegende Mechanismus ist aber noch ungeklärt. Diese Studie untersucht, ob zwischen den Reaktionen von gesunden Probanden auf eine homöopathisch verdünnte Substanz – Aconitum napellus C30 – und auf ein Placebo unterschieden werden kann. **Probanden und Methoden**: Von den 33 Probanden, die an dieser randomisierten, doppelblinden, placebokontrollierten Crossover-Studie teilnahmen, konnten 27 in die Analyse eingeschlossen werden. Die Studie umfasste zwei 7-tägige Behandlungsperioden, während denen jeweils 3 Tage lang das Studienpräparat eingenommen wurde, worauf eine 4-tägige Wash-out-Periode folgte. In einer Gruppe nahmen die Probanden zuerst Aconitum napellus C30 und anschließend Placebo; in der zweiten Gruppe zuerst Placebo und anschließend Aconitum napellus C30. Die Symptome und Erscheinungen vor der ersten und nach beiden Behandlungen wurden gesammelt, bewertet, gewichtet und repertorisiert. Aufgrund dieser Klassifikation wurden die Symptome von dem verblindeten Studienarzt als Effekt der Studienpräparate bewertet, was den Outcome-Parameter der Studie bildete. Die statistische Auswertung der Daten erfolgte mit dem Wilcoxon-Mann-Whitney Rangtest. **Ergebnisse**: Die Crossover-Auswertung zeigte einen statistisch signifikanten Unterschied zwischen Aconitum napellus C30 und Placebo ($p = 0{,}004$). **Schlussfolgerungen**: Zwischen den Reaktionen von gesunden Probanden auf Aconitum napellus C30 und auf Placebo war ein deutlicher Unterschied nachweisbar. Das Crossover-Design mit intraindividuellem Vergleich erwies sich als adäquat beim Erkennen der Studienpräparate und bei der statistischen Analyse mit kleinen Fallzahlen.

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Introduction

Homeopathy is based on the use of extremely diluted solutions of substances which are selected by matching the patient's symptoms with symptoms these substances produce in healthy individuals [1]. Although there are several interesting models to explain the mechanism of action of homeopathic preparations [2–5], this remains largely unknown and is still somewhat controversial. In opposition to the popularity of homeopathy in several countries, most of the clinical trials and meta-analyses of clinical trials performed so far have indicated either lack of efficacy of homeopathic preparations in healing patients or merely a tendency towards efficacy [6–9]. At the experimental level, some studies performed with animals [10, 11], plants [12] or in vitro [13, 14] revealed that homeopathic dilutions may exert biological effects.

The symptoms which are generated by homeopathic preparations can be distinct in different patients even in the context of the same illness. Also, the number and nature of symptoms induced by these preparations in healthy subjects may vary [15]. In homeopathy, the term 'symptom' has a wider meaning than in conventional medicine: it includes all signs in connection with an illness and all reactions reported within a pharmaceutical test [16]. The sum of the observed signs in all tested subjects is associated with a given homeopathic preparation – often called 'symptom totality' – and constitutes the basis for its further use in daily practice. Although this pragmatic approach has proved useful from the perspective of many homeopaths and patients, there has been little research on this approach per se. One difficulty in research on homeopathy concerns the fact that the tools from conventional clinical research have limited use in this conceptually different medical approach.

The present work aimed to clarify whether it is possible to distinguish between the 'symptom totality' reported by healthy subjects shortly after taking a homeopathic preparation – Aconitum napellus C30 – and after placebo ingestion. Whereas this study design originates from conventional clinical research, the method used to define the 'symptom totality' is typical for the homeopathic approach, except that in the present study it was performed shortly after treatment.

Participants and Methods

Participants and Criteria for Study Inclusion

This study was submitted to the cantonal ethics commission of the canton Zurich (KEK) and to the Swissmedic. Execution was approved by both instances. Study participants were recruited among the employees of the Paracelsus Hospital Richterswil, Switzerland. It was planned to recruit 30 healthy volunteers irrespective of sex, socioeconomic origin or ancestry; 33 subjects registered in this prospective, randomized, double-blind, placebo-controlled crossover study. All volunteers signed a written informed consent form. The main instruments used in this study were diaries in which the participants documented every day all symptoms or signs they experienced, and four forms filled in by the researchers during the visits.

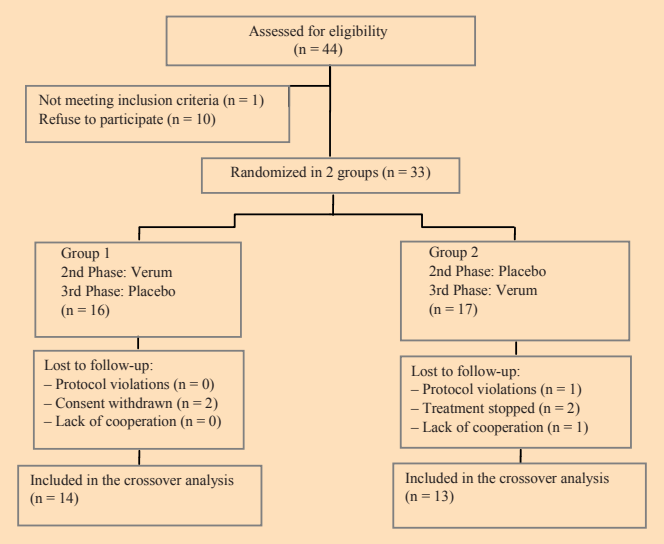

Fig. 1. Flowchart of subject recruitment, randomization, and study completion.

Subjects were asked to use their own words and to be as exact as possible when describing the symptoms in their diaries. Moreover, the diaries included a questionnaire aiming at calling the subjects' attention to as many different items as possible. The written diaries served as a basis for the conversation between researchers and subjects during the visits following the different phases of the study. Diaries 2 and 3, and corresponding forms were used for the assessments of phase 2 and 3 of the study, respectively.

For study inclusion participants had to: 1) be able to understand the study and possible personal consequences, 2) be older than 18 and younger than 65 years, 3) be of good general health, 4) have the possibility of continuing their everyday life during the study, 5) show a negative pregnancy test (female participants). Participants were excluded if they: 1) did not fill in the diaries, 2) experienced any marked change of their life situation during the study, 3) planned or underwent medical treatments or operations during the study, 4) made regular use of medicines for self-treatment, 5) regularly smoked >5 cigarettes/day, consumed alcohol or other drugs, 6) had undergone operations during the 6 months before the study, 7) had taken homeopathic medicaments (>C30) during the 8 weeks before beginning of the study, 8) had used oral contraceptives during the 6 months before beginning of the study, 9) were pregnant or breastfeeding, 10) participated in other homeopathic medicament examinations or clinical studies, or 11) were unable to understand the course and the meaning of the study.

Study Design and Crossover Treatments

The study comprised 3 phases and a follow-up of 14 days after completion of phase 3 (fig. 1, table 1). After a 7-day run-in phase (phase 1), the subjects took the randomized first preparation (Aconitum napellus C30 or placebo) and after a 4-day wash-out (phase 2) switched to the second treatment (phase 3) to complete the 2×7-day crossover design. Sample size was calculated with a power of 80% and an alpha level of 0.05, to comprise 15 cases in each of the two crossover groups.

The study started with the collection of the complete medical history using a homeopathic medical history sheet, followed by the first interview. During the phase 1 (days 1–7), the subjects merely recorded their symptoms in the diaries (Diary 1). Phase 2 started with the intake of the first study substance on days 8–10. During days 8–14 the subjects observed and recorded their symptoms (Diary 2). Phase 3 started with the intake of the second study drug on days 15–17. During days 15–21, again, the

Table 1. Course of the clinical study

	Phase 1		Phase 2		Phase 3		Follow-up
	visit 1 day 1	visit 2 day 7	day 8	visit 3 day 14	day 15	visit 4 day 21	study end day 35
Medical history	x		Start of the first treatment phase		Start of the second treatment phase		
Inclusion and exclusion criteria	x	x					
Informed consent form	x						
Health assessment and clinical analysis		x		x		x	
Release of the diaries	x	x		x			
Collection and assessment of the diaries		x		x		x	
Release of the medication		x		x			
Collection of the medication				x		x	
Adverse events		x		x		x	x
Final assessment							x

subjects documented their symptoms (Diary 3). On day 35, a follow-up (telephone or personal) conversation took place to better detect possible adverse effects. The visits 1–4 took place on days 1, 7, 14, and 21 and the results were recorded with the questionnaires 1–4 which also contained the results of the physical examination.

Given that: 1) the participants had to be able to manage their daily life during the study, and 2) the main study goal was the assessment of short-term symptoms induced by the study substances, and not of the definitive 'symptom totality', the participants were advised to stop the medication as soon as the symptoms developed. For this purpose, the researchers interviewed the participants at days 8, 9, 10, 15, 16 and 17, and were available by telephone during the entire study (7 days per week, 24 h per day).

Study Preparations, Randomization, and Dropouts

Two different preparations were compared: globules of Aconitum napellus C30 (in the text often referred to as verum, i.e. the active substance) and globules of placebo (Spagyros AG, Guemligen, Switzerland). Blinding, randomization and numeration of the globule-flasks were performed by an independent institution (Medidata, Zurich, Switzerland). The globules were taken as follows: 5 globules 3 times daily on days 8–9, and 15–16. The subjects were advised to take the globules at least 30 min before a meal and to let them dissolve slowly under their tongue. If no symptoms were detected on days 8–9 (or 15–16, respectively), subjects were asked to dissolve the globules in 200 ml of water and drink the resulting solution on day 10 (or 17, respectively), about 40 ml every hour until symptoms occurred or the total amount was used.

The study participants were randomized to two groups: group 1 (n = 16) received verum in phase 2 and placebo in phase 3 (verum > placebo); group 2 (n = 17) received placebo in phase 2 and verum in phase 3 (placebo > verum). A total of 6 participants did not complete the program, and had to be excluded from data evaluation (fig. 1). Reasons for drop-outs were withdrawal of consent at the end of the first week (n = 2), stop of study drug after the first treatment phase (n = 2), intake of additional medication (n = 1), and lack of cooperation in the second treatment phase (no diary data, n = 1).

Data Collection and Assessment of Outcome Parameter

A physician trained in homeopathy (D.P.) checked diaries 2 and 3 under blinded conditions and classified the subjects as having received Aconitum or placebo during phase 2 and 3 of the study. In other words, based on the symptoms described in each diary, the physician determined the medication the subject had taken. For this purpose, he evaluated the symptoms according to the homeopathic point of view, i.e. rated and organized them in a repertory. The repertorization was performed using the RADAR 8.1 software (Radar Service, Baar, Switzerland). The assessment of the diaries was performed in the blinded situation, too, but separately, once after phase 2 and again after phase 3. At study completion, the physician compared the results of the two crossover treatments in order to get final assessments of both treatment phases for the statistical analysis.

Statistical Analysis

The null hypothesis was that the investigator's ratings do not differ between the treatment groups. As the study question was one-sided, if the null hypothesis has to be rejected, it can be concluded that verum symptoms are more frequent after intake of Aconitum napellus than after treatment with placebo. The primary outcome parameter, i.e. the assessment of the treatments as either verum or as placebo, was determined for phase 2 and 3, for each group. The difference between the two treatment assessments was coded with –1 (negative treatment recognition), 0 (same assessment in both groups) and +1 (positive treatment recognition), resulting in a 2×3 table. The groups were then analysed by the exact one-sided Wilcoxon-Mann-Whitney test of StatXact, version 5, at a level of significance of $\alpha = 0.05$. A two-sided test was calculated to explore possible carryover effects comparing the sums of the coded values of both treatment phases between the crossover groups.

For an extended interpretation of the results, only the assessments of the first treatment phase (corresponding to parallel group treatments) were tested a posteriori using Fisher's exact test, one-sided, before and after comparing the symptoms/signs experienced by each patient during the two treatments.

Results

Description of Study Subjects

A total of 27 volunteers (18 female, 9 male), all employees of the Paracelsus-Hospital Richterswil, were eligible for data analysis (fig. 1). They were nurses, physicians, laboratory personnel, therapists and employees from the administration; mean age was 41 ± 8.9 years; 14 participants from group 1, and 13 volunteers from group 2 completed both crossover periods.

Table 2. Physician's assessment of which preparations the subjects were taking during study phase 2 and 3

	Treatment assessments			Symptoms classified as verum	
	placebo	verum	total	right	wrong
After phase 2					
Verum treatment					
Count	5	9	14	9 / 14	
Row (%)	35.7	64.3	100.0	64.3	
Placebo treatment					
Count	9	4	13		4 / 13
Row (%)	69.2	30.8	100.0		30.8
After phase 3					
Placebo treatment					
Count	11	3	14		3 / 14
Row (%)	78.6	21.4	100.0		21.4
Verum treatment					
Count	4	9	13	9 / 13	
Row (%)	30.8	69.2	100.0	69.2	
Sum of phases 2 and 3				18 / 27 (66.7%)	7 / 27 (25.9%)

Identification of the Phases

A total of 109 symptoms were described by the subjects during the verum treatment, whereas the number of symptoms mentioned during the placebo treatment was only 36. Considering the study phase 2, the medication was correctly identified in 9 out of the 14 subjects who received the verum and in 9 out of the 13 who received placebo, resulting in a success rate of 18/27 (66.7%). After the second treatment (study phase 3) correct identification was achieved in 9 out of the 13 subjects who had received the verum and in 11 out of the 14 who had received placebo, meaning a success rate of 20/27 (74.1%). Overall, a correct identification of both treatment phases was achieved in 38 out of 54 assessments corresponding to a success rate of 70.4%. Table 2 shows the correct classifications as verum after verum treatment and the false judgements as verum after placebo intake, the latter corresponding to what is generally called placebo effect. These data are also depicted in the right column of table 2 ('symptoms classified as verum').

Statistical Significance of the Data

The results of the Wilcoxon-Mann-Whitney rank test are given in table 3. The mean ranks of the two crossover groups (verum > placebo vs. placebo > verum) differ distinctly ($p = 0.004$). This means it was possible to discriminate between the reactions of healthy subjects to Aconitum napellus C30 and to placebo by using the method of symptom collection and repertorization.

A further test was calculated to control for possible carryover (or residual) effects from the first to the second treatment period (table 3, lower part). This test did not show a trend for statistical significance (mean ranks in both groups were similar).

The data from study phase 2 only (table 1, first treatment period, comparable to a randomized placebo-controlled study design) were submitted to Fisher's exact test, revealing no statistically significant difference between the two groups ($p = 0.53$). Reassessment by the blinded physician at the end of the study, in order to allow for intra-individual comparisons, however, revealed a tendency for good discrimination ($p = 0.074$) when using the same statistical test.

Table 3. Statistical comparison of the outcome parameter between the study groups

Wilcoxon-Mann-Whitney test regarding treatment difference		
	mean rank	significance (one-sided)
Group 1: verum > placebo	10.5	p = 0.004
Group 2: placebo > verum	17.7	
Wilcoxon-Mann-Whitney test regarding carryover effects		
	mean rank	significance (two-sided)
Group 1: verum > placebo	14.6	p = 0.75
Group 2: placebo > verum	13.4	

Discussion

The primary question addressed in the present study is whether the reactions of healthy volunteers to a homeopathic drug – Aconitum napellus C30 – are distinctly different from those to a placebo. Our approach to this question consisted in: a) inviting the study participants to report every symptom they experienced upon treatment with Aconitum napellus C30 and with placebo, following a crossover design, and b) letting the blinded physician determine, on the basis of the symptoms described in the diaries, which treatment the participants had

undergone. The crossover design meets the requirements of today's scientific studies in evidence-based medicine. On the other hand, the volunteers' reactions to the drugs were identified, assessed, rated and repertorized as usually in homeopathy, i.e. according to the suggestions of the founder of homeopathy, the physician S. Hahnemann [17].

The statistical evaluation of our data indicates a clear difference between the reactions to Aconitum napellus and to placebo, whereas the evaluation of the treatment phase before crossing over to the other treatment showed poor discrimination, and the reassessment of this phase at the end of the study only led to a statistical tendency. This suggests that the crossover protocol chosen for this study – at the given sample size – has contributed to the statistically significant result. The short observation period of 7 days and a treatment of only 3 days could have played a role as well. The better discrimination power of the crossover design to compare the reactions of healthy persons to homeopathic dilutions might be also explained by reactions with rather large individual variation, which makes this study design particularly well suited. Furthermore, the final reassessment allowing intra-individual treatment comparisons certainly helped achieve statistical significance. Finally, it is worth mentioning that not only the specificity of the reactions to Aconitum napellus but also the number of symptoms described might have helped achieve correct final assessments allowing intra-individual comparisons of both treatments.

In several previous randomized, blinded, placebo-controlled studies – without crossover design – on symptoms caused by homeopathic dilutions in healthy subjects, no clear difference between the symptoms induced by the homeopathic dilution and symptoms induced by a placebo could be found [18–20]. To our knowledge, to date there are only two publications reporting that the symptoms experienced by healthy volunteers upon the two types of treatment – with a homeopathic dilution and with a placebo – differ [21, 22]. In all, the results of the previous studies and the present work seem to support the advantage of a crossover design when investigating the reactions to homeopathic dilutions. However, care should be taken in extrapolating our conclusions on the reactions to Aconitum napellus C30 to other homeopathic drugs, since these reactions will probably vary with the homeopathic dilution in question. Furthermore, it is conceivable that a parallel group design applied to a much larger sample – all studies mentioned had less than 80 participants – could constitute an alternative to the crossover design.

The major limitation of a crossover design per se concerns the possible effects of the first treatment on the second treatment period, i.e. carryover effects. This limitation should be discussed even if, as in our case, a statistical test reveals no trend for such an effect. In our study, there was a 4-day washout period between the first and the second 3-day treatment. As after intake of Aconitum napellus only short reactions were expected, a 4-day washout period was judged to be sufficient for disappearance of symptoms before the second treatment would begin. In addition, a possible effect of Aconitum napellus taken during the first treatment phase and lasting into the second (placebo) treatment phase would probably result in a verum classification of both periods, i.e. reduce the discrimination power and the chance for statistical significance.

In summary, our study supports the hypothesis that the reactions of healthy subjects to the homeopathic dilution of Aconitum napellus C30 can be distinguished from those to placebo. Furthermore, it suggests that an intra-individual comparison against placebo in a crossover design might be very helpful to investigate the reactions of healthy subjects to homeopathic dilutions.

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