Methodological Standards and Problems in Preclinical Homoeopathic Potency Research

Article *in* Forschende Komplementarmedizin · March 1998

DOI: 10.1159/000021071 · Source: PubMed

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Forsch Komplementärmed 1998;5:27–32

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Key Words
Methodology · Preclinical research · Homoeopathy · Anthroposophical medicine · Homoeopathic dilutions · Potencies

Summary
If clinical evidence for the effectiveness and specifity of homoeopathic potencies further accumulates, preclinical research into the nature of homoeopathic dilutions will develop into an important research area of pharmacology. General methodological standards for preclinical investigations of homoeopathic potencies are discussed in order to improve the quality of future research. Beside the classical standards of the experimental sciences, special attention has to be given to the preparation of homoeopathic potencies and corresponding controls. A combined use of i) agitated but not diluted solvent and ii) untreated solvent is proposed as the most appropriate control within an investigation into possible effects of homoeopathic potencies.

Schlüsselwörter
Methodologie · Präklinische Forschung · Homöopathie · Anthroposophische Medizin · Homöopathische Verdünnungen · Potenzen

Zusammenfassung
Methodologische Richtlinien und Probleme in der präklinischen Erforschung homöopathischer Potenzen
Wenn sich die Hinweise auf eine spezifische Wirksamkeit homöopathischer Potenzen in der klinischen Forschung weiter verdichten, werden sich präklinische Untersuchungen, welche die Gesetzmässigkeiten der homöopathischen Potenzen zu erfassen suchen, zu einem bedeutenden Zweig der Pharmakologie entwickeln. Um die Qualität zukünftiger Arbeiten in diesem Gebiet zu steigern, werden allgemeine methodologische Richtlinien zur präklinischen Potenzierforschung vorgestellt und diskutiert. Neben den allgemeinen Regeln der Experimentierkunst ist hierbei besonderes Augenmerk auf die Herstellung der homöopathischen Potenzen und der entsprechenden Kontrollen zu richten. Als geeignetste Kontrolle für den Nachweis homöopathischer Potenzwirkungen wird ein kombinierter Einsatz von i) verschütteltem, aber nicht verdünntem Lösungsmittel sowie ii) unbehandeltem Lösungsmittel vorgeschlagen.

Introduction

Homoeopathy and anthroposophical medicine are currently under investigation in a steadily growing number of clinical trials. This scientific progress is complemented by intense discussion of scientifically sound methodologies for clinical research in homoeopathy and anthroposophical medicine that will be acceptable to both complementary and mainstream conventional medicine [1–10]. Homoeopathic drug preparations have also been subjected to a huge number of preclinical investigations [11–15]. Unfortunately the necessary supplementary discussion of methodological problems in preclinical research in homoeopathic potencies is far less advanced [16, 17].
This is hard to understand, since preclinical research into the nature of homoeopathic dilutions is as important as clinical observations and trials. This view is supported hy the interpretation of the hitherto largest meta-analysis of clinical trials in homoeopathy, where the authors state: '… we would be ready to accept that homoeopathy can be efficacious, if only the mechanism of action were more plausible' [7]. Preclinical research in high dilutions which aims to investigate the 'mechanism of action' therefore holds a key position in the general research programme in the realm of homoeopathy and anthroposophical medicine.
Practitioners in homoeopathy or anthroposophical medicine use homoeopathic potencies as specific medicines, i. e. they presuppose that homoeopathic preparations do have a specific nature and may therefore induce a specific reaction from the patient, if the medicament meets the unique characteristics of the individual patient and his illness. The claimed specific nature of homoeopathic dilutions

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is questioned, however [18, 19]. This is due to the special nature of homoeopathic potencies which are prepared by successive exponential dilution and agitation of a mother tincture in a solvent. Dilution may go so far that according to Avogadro's number the probability of finding a single molecule of the mother tincture in a homoeopathic preparation is virtually zero.

Research that reports on preclinical effects of homoeopathic potencies will be thoroughly and critically analysed, since an observable and reproducible action of higher homoeopathic dilutions can hardly be explained by the present body of scientific theories and the wide-spread materialistic philosophy of life and nature. Scientists may be forced to accept new basic concepts and laws in the realm of the general modes of action in nature. It is therefore clear that any such preclinical research has to meet the highest scientific and methodological standards, since positive results may lead to a true revolution in science and philosophy. It also has to be kept in mind that the acceptance of any such new basic concepts by the majority of active scientists is not just the sum of individual scientific insight and understanding, but rather a very complex psychological and sociological process [20]. To overcome the problems associated with the latter, the scientific basis must be particularly sound and absolutely beyond doubt.

After the pioneering work of L. Kolisko [21, 22] which was stimulated by R. Steiner in 1920 [23], hundreds of preclinical studies of homoeopathic potencies have been published in the last decades. The quality of these studies is judged rather differently, however. Some reviews end up with a considerable number of 'good' studies [11, 12]; with others the conclusion is that only few studies are acceptable by today's scientific quality standards [13–15]. One is thus forced to conclude that the term 'scientific quality' can be rather ambiguous. This applies not only to scientists who do experimental research, but also to those active in meta-analysis.

It seems justified, therefore, to summarize, update and discuss the most important methodological points for preclinical investigations of the reality and nature of homoeopathic potencies. In section 2 some rather general remarks concerning design and setup of homoeopathic model systems will be given. Section 3 deals with production standards for homoeopathic dilutions and section 4 with appropriate controls. Section 5 closes with a summary of the main points.

We wish to stress at this point that this paper deals only with the methodological questions connected with research into the homoeopathic drug manufacture, i. e. 'potentisation' by serial dilution and agitation. We do not consider other important methodological problems which open up when investigating e. g. the homoeopathic Law of Similars, homeopathic drug provings or specific ideas about the nature of homoeopathic potencies [12, 24, 25].

Design of Homoeopathic Model Systems

The practicioners' claim is that homoeopathic potencies do have specific nature and are not simply placebo. Thus the fundamental null hypothesis in preclinical homoeopathic research may be as follows:

H_0: Homoeopathic potencies do not have specific nature and cannot be distinguished from appropriate controls.

If this null hypothesis H_0 can be rejected by statistical analysis of experimental results we are forced to state the contrary H_1:

H_1: Homoeopathic potencies do have specific nature and can be distinguished from appropriate controls.

The question of situation-adopted controls for homoeopathic potencies is discussed in section 4. For the moment it is assumed that such controls exist. The next step is to test the null hypothesis. This is a classical question in the experimental sciences and can be investigated by experiments, i. e. model systems of nature in which the researcher tries to vary only the parameters in question and to fix all other parameters. This is a necessary condition in order to definitely conclude that any difference observed between several treatment groups is due to these treatments and not to any other influence. These remarks may sound obvious, but experience shows that this fundamental precondition of experimental investigations is often ignored.

General Experimental Rules

An experimental system has to be free of uncontrollable side effects. This implies that the influence of any changing boundary condition can be either 1) excluded, 2) monitored and corrected or 3) randomized.

Any given homoeopathic dilution must be compared in its action against one or several controls. Since any external influence manifests in space and time, the ideal comparison would happen simultaneously at the same location. This is not feasible, however. But it is possible and advisable to minimize any spatial and temporal difference in order to improve the stability of the experimental system.

Common external influences are light, temperature and humidity. The importance of these factors for biological systems is evident, yet they are sometimes ignored. Greenhouses always have light and temperature gradients, growth chambers may have a warmer side and phytotrons a wet corner, temperature drift during sample preparation may have a differential influence on samples, measuring instruments usually have time and temperature drifts, etc. Other external influences may be due to electromagnetic fields, soil quality in field and greenhouse experiments, seed quality, etc. Less widely known but equally important are chronobiological effects which manifest on timescales from seconds to years [26–29]. The possibility of unconscious influences by the researcher is also evident. All these possible side effects may seriously hamper an experimental design. It is therefore absolutely necessary to make provision for the stability of any experimental system.

It is generally assumed that unconscious or semi-conscious influences by the researcher on an experimental system can be excluded by coding the different experimental conditions. Thus the very first rule is that all manipulations and measurements have to be carried out blind. But it would be rash to state that such a procedure totally excludes the possibility of influences by the scientist who does the experiment. There are phenomena in clinical research which show that the degree of information a patient possesses may change the results of double-blind clinical trials [30]. Correspon-

ding experiments in preclinical research will have to show if such effects might also be relevant in this area of research.
As already mentioned, influences due to changing external conditions have to be excluded, corrected or randomized. The question as to which boundary conditions are critical for a given experimental design cannot be answered in general; some examples have been given above. In any case the stability of the experimental system in question must be meticulously assessed. A necessary overall test consists of blind runs, comparing the results of several experimental conditions, all of them controls, in a typical setup. The results must be statistically equivalent, i.e. the null hypothesis (all conditions are equal) should not be rejected. It would be desirable to show the results of such control runs in a given publication to document the quality and credibility of the experimental design.
An example for this procedure may be as follows. A screening of homoeopathic potencies is planned in a plant growth system, measuring plant height and weight. There is a total of 200 plants, with 20 plants per experimental condition. Running such an experiment with 200 plants under exactly the same control conditions (e. g. water instead of homoeopathic potencies) must yield statistically identical results in all dependent parameters (e. g. height and weight) for all 10 groups of 20 plants which represent the independent parameters.

Statistical Design and Data Evaluation
Planning and design of any preclinical homoeopathic study should be guided by common statistical standards in the experimental sciences [31–34]. It is advisable to distinguish between screening tests, preliminary investigations and main studies; adapted statistical designs exist for all purposes. Care must be taken to look for differences not only in mean or median, but also in other parameters that describe measured data distributions such as standard deviation, skewness, etc. Statistical methods to investigate all properties of a given data set are available both for parametrical [31, 34] and for non-parametrical methods [35]. Critical preconditions for the different statistics should be carefully checked. If one is not sure as to which method to choose, a statistician's advice can be very helpful, saving time, money and energy.

Reproducibility
Exact reproducibility of a given effect is only possible if all conditions which are critical for the effect are exactly the same on reproduction of an experiment. Strict reproducibility of an effect therefore must not be required dogmatically [36, ch. 2.3]. Reproductions of an experiment rather serve as a tool to determine which experimental conditions play a necessary, modifying or unimportant rôle in the occurrence of a certain phenomenon.
As already mentioned, time-dependent pharmacological phenomena are quite common [27, 28]. Any such effect within homoeopathic preclinical studies therefore is not a reason to deny the reality of an action of homoeopathic potencies, but an interesting phenomenon to study. But this is only possible if single experiments have already given statistically significant results. Since there are some indications that homoeopathic effects in preclinical systems might be time-dependent [37–40], we explicitely recommend to study a given system's response to homoeopathic potencies as a function of time.
If it is not possible to reproduce the results of one laboratory in another laboratory, this does not automatically mean that the results of one or the other laboratory are 'wrong' [41, 42]. This is of course possible; but it has to be kept in mind that many purely physical effects depend on certain, not always directly perceptible properties of space such as electromagnetic fields or gravitation. Since one does not know which conditions might be critical for the occurrence of homoeopathic effects, a meticulous study of all possible reasons for a given discrepancy between several laboratories is advisable before rushing to conclusions.

Ethical Aspects
One of the – not only to the public – most appealing aspects of homoeopathy and anthroposophical medicine is that they do not rely on painful or invasive animal experiments in the process of drug investigation and development. We therefore argue that such experiments should be either avoided or at least limited to very important research aims that cannot be investigated by other methods.

Publication Standards
It is very helpful for the reader of a given trial's publication to be fully informed on the general scope of the study undertaken. Was the aim of the work presented a crude screening to determine which substances at which potency levels might influence a given experimental system? Did a screening precede the presented study? What reason, if any, motivated the selection of the system, potencies and potency levels used?
The experimental system has to be described in detail. It must be possible for another researcher to reproduce the experimental design in order to test the reproducibility of the claimed results. It is also absolutely necessary to give full details of the performed statistical methods and their results. All critical preconditions for the statistical methods used should be carefully checked and documented. It is also very helpful to indicate the typical standard deviations of all dependent parameters, i.e. types of measurement. This information helps the reader to check the statistical evaluation of the data.

Preparation of Homoeopathic Drugs

If it is assumed within a preclinical study of homoeopathic potencies that they are not just logarithmic dilutions, but pharmaceutical preparations with a specific action, the preparation process must play a critical role. In general it seems reasonable to base the production of homoeopathic potencies on established pharmaceutical procedures.
But it is also absolutely necessary to standardize, carefully document and publish in every possible detail the preparation of the homoeopathic drugs and controls used [17]. It is definitely not sufficient to simply refer to established methods such as the German Homoeo-

pathic Pharmacopoeia, since only few critical parameters are clearly defined there. As long as one does not know which preparation conditions of homoeopathic potencies are essential and which not, it is absolutely necessary to report the production process in detail.
The following list of critical points is limited to fluid potentisation; generalisation to solid state potentisation is easily possible.

- Mother tincture: what is its characterisation? Are analytical data available? What was its age at the beginning of potentisation? Was it produced by dissolution, extraction, fermentation, etc.? What solvent was used (water, alcohol, acid or salty solutions, etc.)?
- Diluent: what are its characteristics? How was the solvent prepared (distilled, double-distilled, de-ionized, etc.)? Was it always the same during the production process (water, alcohol, mixture, other fluids, etc.)? If it was changed during drug preparation, at what potency level was the change made? Are analytical data available?
- Potentisation vessels: of what material were the vessels composed (glass of what quality, polystyrol, polypropylene, polyethylene, etc.)? What form was used? What was the ratio of agitated material to vessel volume? Have the vessels been used earlier to produce other homoeopathic potencies? If yes, how were the vessels cleaned?
- Contamination: what precautions have been taken to exclude contamination by other substances? Is it possible to rule out cross contamination by other potencies?
- Agitation and dilution: was agitation performed manually or by a machine? What type of movement was used (horizontal or vertical, free movement in space or striking a surface, etc.)? How intense was the agitation (magnitude of movement, agitation frequency, etc.)? How was the agitation interval defined (number of strikes, length of agitation, etc.)? What sort of fluid movement was aimed at (laminar or turbulent flow, small or large scale eddy flow, etc.)? How long is the rest interval between agitation and the next dilution step and between dilution and the succeeding agitation? What is the typical error for the dilution factor?
- Other parameters: what was the age of the potencies at the beginning and the end of the experiment? Was it the same for all experimental conditions? What type of vessels were used for storage, if any? Are there any analytical data to be reported for the potencies (especially important for lower levels)?

Adequate Controls

To evaluate the action of homoeopathic potencies it is necessary to compare their action to corresponding controls. Since the nature of the former is not yet known, definition of the latter is not yet completely determined either. It is therefore advisable to include several controls in a given experiment in order to increase the information gain. We again limit our discussion to fluid potentisation.

Pure Solvent

Pure solvent as single control cannot be recommended, since any observed difference between a given homoeopathic drug and this control could simply be due to a different physicochemical state and therefore be explained by known physical and chemical laws. During agitation some material from the vessel walls may dissolve in the fluid. This effect is especially pronounced for glass ions [43–45], but plastics may also release incorporated substances such as plasticizers [46, 47]. During agitation, air is dissolved in the fluid. This changes not only the solvent pH but also other physicochemical properties that may be relevant for both physicochemical measurements and biological systems.
Different types of controls have been proposed to exclude such effects – potentised solvent, agitated solvent, 'merely diluted' (but not potentised) homoeopathic drugs and non-specific homoeopathic potencies. Advantages and drawbacks of these different approaches are discussed below.

Potentised Solvent

A control treated in exactly the same way as a homoeopathic drug may account for all the physicochemical factors mentioned above. This implies that a homoeopathic dilution is prepared according to standard procedures, except for the first dilution step where the homoeopathic drug is replaced by the solvent itself: one thus gets potentised solvent.
At first glance, this might be a perfect control for any homoeopathic dilution. But this is only true if the potentised solvent itself has no 'homoeopathic action'. Since alcohol and certain mineral springs are listed in homoeopathic repertories, the assumption of a perfect control without 'homoeopathic action' may be faulty and misleading. One will therefore be well advised to judge results of such controls in an unbiased way.

Agitated Solvent

The dilution step seems to be a necessary part of making a homoeopathic preparation; the above-mentioned physicochemical artefacts are associated with the agitation step only, however. One therefore may raise the idea of a control wich consists of agitated but not diluted solvent. Since 90% or 99% (depending on D (×) or C potentisation) of the material of a given homoeopathic potency consists of solvent that has undergone agitation only once, it may be sufficient to agitate the control only once, i. e. in the same way as the last potentisation step was performed. The action of dissolved vessel wall substances and incorporated air may be somewhat weaker in such a control than in a homoeopathic drug, since 10% or 1% (corresponding to D (×) and C potencies) of the solvent of a homoeopathic dilution was agitated twice, 1% or 0.1% three times etc.
The following procedure may be adopted to establish a difference in action between homoeopathic potency and agitated solvent as control:

1) if agitated and non-agitated solvent do not differ in their action on the used model system, vessel substances and air do not seem to influence the model system. The homoeopathic drug may then be referred to either control;
2) if the action of agitated solvent differs from untreated solvent by an amount δ, the action of a homoeopathic drug has to show a statistically significant difference from agitated solvent with an

additional security factor of $0.11 \times \delta$ for D (×) potencies and $0.01 \times \delta$ for C potencies in order to exclude the effect of multiple physicochemical agitation effects.

Dilution without Agitation

In order to differentiate the homoeopathic potentisation process from normal dilution, it has been proposed to include dilution without agitation in the experimental design [12, 15].

This approach has severe drawbacks, however, since it is practically impossible to produce a homogeneous dilution without any agitation or eddy production. One would have to rely on a pure diffusion process which is known to need a lot of time to produce a homogeneous mixture of fluids. It is a nice and very instructive experiment to track the distribution of a drop of ink or another stain in a glass of water. It may be concluded that some eddy production is necessary to obtain a homogeneous dilution. We therefore argue that no dilution produced without agitation serves as a control for a homoeopathic potency, being in fact a homoeopathic potency, though a 'bad' one compared to standard procedures in homoeopathic pharmacy.

Additionally the physical conditions which determine air incorporation and the dissolution of vessel wall substances are not at all comparable if the agitation step is omitted. One therefore has no control over these physicochemical factors. This point is especially important in experiments with homoeopathic dilutions where the concentration remains within the realm of material effects. There may be purely physicochemical differences between potencies and controls due to differential vessel wall adsorption, inhomogeneous mixture, precipitation, agglutination and denaturation.

So it seems that the idea of 'dilution without agitation' is not a general control to study and define the action of homoeopathic potencies. It rather belongs to the question which homoeopathic production procedures yield optimal pharmacological results.

Nonspecific Homoeopathic Potencies

Since anthroposophical medicine and homoeopathy claim to use higher homoeopathic potencies as specific information for an ill, i. e. mis-informed, organism and not as medicinal agents with material effects such as in conventional medicine, the idea was raised to use the specificity of information of a given homoeopathic potency to distinguish its action from other nonspecific homoeopathic potencies which do not offer relevant information in the given experimental context [48]. One therefore might compare the action of several homoeopathic potencies in an experiment, where the potencies differ either in potency level or in mother tincture. If these potencies are prepared in the same way, but differ in their experimental impact, one would indeed conclude that some homoeopathic potencies had a specific effect that could not be due to physicochemical artefacts. But an experimental design of this type demands a higher degree of a priori understanding of the interaction between preclinical system and investigated potency.

If the experimental design does not include other controls, some drawbacks can be stated. If several different potencies had an identical effect in an experiment, this impact would not be detected. This would lead to false-negative results. In such an experimental design (without additional controls) it is also only possible to study the difference between different items of information, but not the action of any information or no information at all. Together with other controls, however, the use of nonspecific potentised substances as control may be very informative.

Summary

In order to detect the action of a homoeopathic potency that cannot be reduced to physicochemical artefacts, a combination of i) solvent that has heen agitated once but not diluted and ii) untreated solvent seems to be the most adequate control.

The specificity of any given homoeopathic potency can be investigated hy introducing other homoeopathic potencies. Potentised solvent is only one possibility. Such an additional control increases the information gain of an experiment.

The use of 'only diluted' and not agitated homoeopathic potencies may yield information about different manufacturing methods of homoeopathic medicines, but is of no use as a control for the action of a homoeopathic potency.

In clinical research a consensus conference came to the agreement to use only untreated solvent as placebo because of financial and ethical reasons [10]. In preclinical research, however, we think that the use of at least two controls is justified and necessary, because the probability of purely physicochemical artefacts is much larger and because financial and ethical constraints are less pronounced.

Conclusion

The most important points to ensure the highest scientific quality for preclinical studies of homoeopathic potencies may be summarized as follows:

- careful planning and design of the experiments
- blind manipulation and measurements
- blind runs of the typical experimental design (typical standard deviations)
- detailed description of the production process for homoeopathic potencies
- reasonable and adapted controls
- several reproductions of a given experiment
- careful statistical analysis of the experimental data
- unprejudiced interpretation of all results.

Any preclinical research in homoeopathic potencies that does not respect these basic requirements of good scientific methodology is of little use for further scientific development.

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