Research Article

Effects of homoeopathic ultrahigh dilutions of Aconitum napellus on Baker’s yeast-induced fever in rabbits

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ABSTRACT

OBJECTIVE: To evaluate the effects of homoeopathic ultrahigh dilutions of Aconitum napellus in Baker’s yeast-induced fever in rabbits.

METHODS: Rabbits were divided into 4 groups and each group contained 6 rabbits. Baker’s yeast suspension (20%) was injected subcutaneously. After fever induction, paracetamol and homoeopathic ultrahigh dilutions (A. napellus 200c and 1 000c) were given orally. Rectal temperature was measured with digital thermometer hourly.

RESULTS: Fever was induced in all the rabbits after 4 hours of Baker’s yeast administration. A. napellus 200c and 1000c significantly reduced the temperature (P < 0.05). In positive control, temperature decrease was more significant (P < 0.001).

CONCLUSION: The above findings indicate the effectiveness of ultrahigh dilutions of A. napellus in Baker’s yeast-induced fever in rabbits. However, the effects were slower and less significant than standard medicine. Moreover, future research is required to know their mechanism of reducing temperature.

Keywords: Aconitum napellus; antipyretic; homeopathy; ultrahigh dilutions


1 Introduction

Fever is a complex response that can be produced by a wide variety of infectious organisms and may also occur during non-infectious inflammatory conditions. The primary manifestation of fever is an elevation of body temperature, usually by 1 to 4 °C.[1] Whenever body finds any infectious agent, its natural defense system is activated to create an environment where an infectious agent or damaged tissue can not survive.[2] Fever, in fact, is not a disease itself, but it is the symptom of other pathological states and the immune response of the body that attempt to neutralize microbial infection in the body. Increased temperature leads to the disturbance of the human physiology and causes patient discomfort.[3]
There are various antipyretics to control fever such as paracetamol. It reduces fever in multiple species including rabbits; however it has certain side effects such as asthma, hepatotoxicity and hypertension.\textsuperscript{[4–7]} Thus, it is imperative to find therapeutic alternatives for fever.

Homoeopathy is based on similia principle, “similia similibus curentur” that means to treat with something that can produce an effect similar to the suffering.\textsuperscript{[9]} Homoeopathic medicines in nontoxic dilutions are administered to healthy people (volunteers). These medicines cause reversible symptoms on the physical, mental and psychic level of volunteers which are systematically detected and recorded by the provers and the investigators. The symptoms appearing in a homoeopathic pathogenetic trial is named as the “remedy picture” of the particular homoeopathic medicine being tested. This information is subsequently organized into the homoeopathic materia medica. In the clinical practice, homeopaths choose homoeopathic medicines by comparing these remedy pictures with the symptoms presented by the patient.\textsuperscript{[9]} Thus, the homoeopathic medicines are selected on the similarity between drug-specific pathogenesis “remedy picture” and disease-specific individual status.\textsuperscript{[10]}

In homoeopathy, remedy picture of Aconite in fever is high-grade fever of acute and sudden onset that can be due to the exposure to cold winds, fear or some inflammatory condition.\textsuperscript{[11]}

The study was conducted on “Baker's yeast-induced fever model” of rabbits. In the experimental studies, Baker's yeast (\textit{Saccharomyces cerevisiae}) causes fever in animals in large doses (intraperitoneal or subcutaneous administration).\textsuperscript{[12,13]} It causes high-grade fever in a very short period. Some studies have shown that \textit{S. cerevisiae} and constituents of its cell wall, such as mannans, caused fever that is accompanied by an increase in the plasma levels of tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), interleukin-1\(\beta\) (IL-1\(\beta\)) and interferon-\(\gamma\) (IFN-\(\gamma\)).\textsuperscript{[14,15]} Thus, disease-specific pathogenesis of Baker's yeast-induced fever is high-grade infective fever of acute onset that is caused by injecting a large quantity of Baker's yeast.

In this study, medicine was selected on the basis of some similarity between disease-specific pathogenesis of Baker's yeast-induced fever and drug-specific pathogenesis or “remedy picture” of Aconite.

In many countries and universities, research in homoeopathy and its ultrahigh dilutions is a topic of interest. Treatment with homoeopathic medicines is assumed as the placebo effect. But different studies revealed that homoeopathic medicines are effective in different diseases.\textsuperscript{[16–23]} It is also assumed that homoeopathic medicines are slower in action and does not work in acute conditions like “fever”. The study aimed to evaluate the effectiveness of ultrahigh dilutions of \textit{Aconitum napellus} in fever.

2 Materials and methods

2.1 Animals

Animals (female and male) used in this study were local strain rabbits (1.0–1.7 kg). Animals were accommodated under controlled environmental condition (23–25 °C) in the animal house of Khawaja Fareed Campus, Faculty of Pharmacy and Alternative Medicine, the Islamia University of Bahawalpur, Pakistan. They were acclimatized to animal house conditions for 7 d before the start of the experiment. They were also habituated to handling temperature measurement procedure and injection stress. The animals were provided with standard food and tap water ad libitum. They were fasted 24 h before the trial but were given free access to water. The experimental protocol regarding current study was approved by the Pharmacy Research Ethics Committee (PREC) meeting held on September 15, 2015 via Notification Number 89-2015/PREC dated of the Department of Pharmacy, the Islamia University Bahawalpur, Pakistan. Rabbits were selected for this study because this animal is not aggressive and docile and comes under the purview of local ethical committee as it is included in small animal category.\textsuperscript{[22]}

2.2 Medicines, reagent and apparatus used

Paracetamol (GlaxoSmithKline, Pakistan, Limited) and \textit{A. napellus} 200c and 1 000c (Dr. Willmar Schwabe GmbH and Co. KG, Germany); Baker’s yeast (Rossmoor food products, Karachi, Pakistan); Digital Thermometer (Medisign MANA & CO Pakistan).

Homeopathic ultrahigh dilutions are mostly diluted according to centesimal scale (1 : 99 = 100, one part drug and 99 part solvent) denoted by Roman numeral C or c. When remedy is denoted by 200c or 1 000c, it means 200th or 1000th dilution respectively prepared under centesimal scale (1 : 99 ratio).

2.3 Experimental setup

Rabbits were divided into 4 groups consisting of 6 rabbits in each group as follows:

- **Group 1**: Negative control animals (received 10 drops of 90% succussed alcohol in 1 mL distilled water by oral administration). 90% succussed alcohol was used as negative control because all the used medicines were prepared in it (as a vehicle) as per company mentioned.
- **Group 2**: Standard control animals (received 150 mg/kg paracetamol by oral administration).\textsuperscript{[23]}
- **Group 3**: \textit{A. napellus} 1 000c (received 10 drops of \textit{A. napellus} 1 000c in 1 mL distilled water by oral administration).
- **Group 4**: \textit{A. napellus} 200c (received 10 drops of \textit{A. napellus} 200c in 1 mL distilled water by oral administration).

2.4 Antipyretic activity

2.4.1 Pyrexia induction

Antipyretic activity was done by method of Hossain et al.\textsuperscript{[23]} with slight modifications. Pyrexia was induced by...
subcutaneous injection of 20% suspension of Baker’s yeast in 0.9% saline (3 mL/kg). Rabbits with temperature raise of 0.5–2.0 °C were included in study.[13]

2.4.2 Body temperature measurement
Rectal temperature of rabbits was measured with digital thermometer coated with glycerin (lubricant). Rectal temperature was recorded one hourly for 6 h.

2.4.3 Medicine administration
Four hours after yeast injection, the animal groups received medicines orally (single dose). Experimenters were not blinded to experimental groups. However, statistician was blinded (only codes for each group were mentioned with recorded readings of each group).

2.5 Statistical analysis
Results were analyzed by SPSS version 20.0 software. Data were expressed as mean ± standard error of mean. Statistical significance among groups was analyzed by one-way analysis of variance for each time point (between the groups) followed by LSD post-hoc test. $P \leq 0.05$ was considered significant.

3 Results
At the 4th hour after yeast administration, temperature was raised in all rabbits. The temperature variations in the groups at different hours were as follows.

3.1 Effects of vehicle on fever induced by Baker’s yeast
The negative control group showed a continuous increase of temperature till the 8th hour from the time of yeast administration and then showed the progressive decline in temperature. At 0 hour, normal mean temperature of the group was (39.20 ± 0.31) °C. Up till the 8th hour, a temperature raise of 1.30 °C was observed that started to decline afterward (Table 1).

3.2 Effects of paracetamol on fever induced by Baker’s yeast
At the 4th hour after yeast administration, 1.0 °C temperature increase was observed. Paracetamol was administered orally at this time, and this group showed the decrease of 1.1 °C temperature in the 1st hour of medicine administration ($P < 0.002$). At the 2nd hour of medicine administration, a further decrease of 0.1 °C temperature was observed ($P < 0.001$). In the succeeding hours temperature decrease continued (Table 1).

3.3 Effects of A. napellus 1 000c on fever induced by Baker’s yeast
A. napellus 1 000c group showed an increase of 1.1 °C 4 hours after yeast administration. A slow decrease of temperature was observed that became significant in the 3rd hour after medicine administration ($P < 0.01$). The effect was more significant than Aconite 200c but slower as compared to paracetamol (Table 1).

3.4 Effects of A. napellus 200c on fever induced by Baker’s yeast
A. napellus 200c group showed an increase of 1.3 °C 4 hours after yeast administration. After the 3rd hour of medicine administration, temperature decrease became significant ($P < 0.05$) but the effect was slower as compared to paracetamol (Table 1).

4 Discussion
Homoeopathy is one of the most popular complementary and alternative system of medicine.[24] Despite this popularity, homoeopathy faces many criticisms. The main obstacle to consider homoeopathy is the supposed “implausibility” of biological activities for homoeopathic potencies beyond Avogadro’s number.[25] The present study reported the effects of Aconite (higher potencies beyond Avogadro’s number of molecules) in Baker’s yeast-induced fever in rabbits.

In the present study, administration of Baker’s yeast in rabbits caused a significant elevation of temperature in 4 h. This finding is in conformity with previous studies reporting

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<tr>
<th>Table 1</th>
<th>Effects of Aconitus napellus on Baker’s yeast induced fever in different hours of study</th>
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<tr>
<td><strong>Group</strong></td>
<td><strong>Rectal temperature before medicine administration (°C)</strong></td>
</tr>
<tr>
<td></td>
<td>0 hour</td>
</tr>
<tr>
<td>1</td>
<td>39.20 ± 0.31</td>
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<tr>
<td>2</td>
<td>39.50 ± 0.86</td>
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<tr>
<td>3</td>
<td>39.60 ± 0.16</td>
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<td>4</td>
<td>39.20 ± 0.16</td>
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* $P \leq 0.05$, ** $P \leq 0.01$, vs control group. Values are expressed as mean ± standard error of mean ($n = 6$). 0 hour reading is normal temperature of rabbits before yeast induction. Before treatment 4 hour reading is after fever induction reading. Group 1: negative control animals (received 10 drops of 90% succussed alcohol in 1 mL distilled water by oral administration). Group 2: standard control animals (received 150 mg/kg paracetamol by oral administration). Group 3: A. napellus 1 000c (received 10 drops of A. napellus 1 000c in 1 mL distilled water by oral administration). Group 4: A. napellus 200c (received 10 drops of A. napellus 200c in 1 mL distilled water by oral administration).
fever induced by Baker’s yeast in rats and rabbits. In the classical model of fever pathogenesis, fever induction is started by the release of pyrogenic cytokines such as IL-1, IL-6, TNF and interferons into the blood due to exogenous pyrogens. S. cerevisiae and constituents of its cell wall, such as mannans, cause fever that is associated with increased plasma levels of IL-1β, IFN-γ and TNF-α. These mediators act on central nervous system (CNS) at the level of organum vasculosum of the lamina terminalis. They induce prostaglandin synthesis that is the primary mediator of fever. In this study, orally administered paracetamol at a dosage of 150 mg/kg significantly diminished Baker’s yeast-induced fever in rabbits. Paracetamol has the action on a specific cyclooxygenase (COX) isoenzyme in the CNS. Results are in line with other studies.

The experimental model used in this study to evaluate antipyretic action has explored what is allopathically indicated as pharmacological action on one symptom (e.g., temperature reduction). While paracetamol has the action on COX isoenzyme in the CNS, homoeopathic medicines have supposed action on the regulation of inflammatory pathological changes as the phenomenon by itself is seen as an expression of allostatic mechanism of the organism. If highly diluted homoeopathic medicines act through an influence on allostatic mechanism of the organism, at least theoretically, this action could be very sensitive to smallest changes in experimental conditions.

Temperature reduction effect could not reflect the full potential of the homoeopathic treatment of fever according to classical homoeopathy. A homoeopathic medicine are not selected on the basis of local symptoms but the global pathophysiological characteristics of the individual is considered. Aconite is useful homoeopathic remedy for high-grade fever that has an acute onset usually after stress or cold exposure. In the present study, Aconite decreased temperature significantly (although number of rabbits were too small to draw fair conclusion) perhaps due to their some similarity with Baker’s yeast-induced fever (high-grade fever of acute onset). But the medicine is lacking similarity regarding fever type, i.e., infectious fever. Partial similarity might be responsible for slower temperature decrease as compared to paracetamol, as Aconite usually treats fever caused by stress or cold exposure.

The effects of A. napellus should be evaluated on different models of fever especially in stress-induced hyperpyrexia model. Moreover, the antipyretic effects of other homoeopathic medicines used for infectious fever types (Belladonna and Pyrogenium) should be evaluated in Baker’s yeast-induced fever model. It might be suspected that Belladonna and Pyrogenium could show more potent antipyretic effects against Baker’s yeast-induced fever. The effects of A. napellus on pyrogenic cytokines should be evaluated so that the mechanism of action of these medicines in fever could be clear.

5 Conclusion

From the present experiment, it becomes evident that ultrahigh dilution of the homoeopathic medicine A. napellus is capable of rendering antipyretic activity against Baker’s yeast-induced fever in rabbits (although number of rabbits was too small to draw fair conclusion).

6 Competing interests

The authors declare that they have no competing interests.

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Submission Guide

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