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Original Research Article

In vivo evaluation of antipyretic effects of some homeopathic ultra-high dilutions on Baker's yeast-induced fever on Similia principle

Saeed Ahmad ^{a, b}, Tayyeba Rehman ^{b, *}, Waheed Mumtaz Abbasi ^b^a Department of Pharmacy, Faculty of Pharmacy and Alternative Medicine, The Islamia University of Bahawalpur, Bahawalpur, Pakistan^b University College of Conventional Medicine, Faculty of Pharmacy and Alternative Medicine, The Islamia University of Bahawalpur, Bahawalpur, Pakistan

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ABSTRACT

Background: Homeopathy is a controversial alternative system of medicine. The action of homeopathic medicines is considered slow and it is assumed that homeopathic medicines are ineffective in acute conditions such as fever.

Objective: In the present study, effects of 3 homeopathic medicines on baker's yeast induced fever were investigated.

Materials and methods: 42 local strain rabbits were equally divided into 7 groups. Normal saline was orally administered to group 1 (normal control) rabbits without fever induction. Group 2 underwent baker's yeast-induced fever (negative control). Groups 3, 4, 5, 6 and 7 underwent baker's yeast-induced fever and were thereafter treated orally with paracetamol, *Nux vomica* 200C and 1M, *Calcarea phos* 200C and *Belladonna* 200C respectively. Rectal temperature was checked hourly. The abdominal writhing and frequency of loose stools were also monitored. ANOVA was applied for checking statistical significance. $p \leq 0.05$ was considered significant.

Results: The rectal temperature increased significantly ($p < 0.05$) in the negative control group when compared to the normal control. Abdominal writhing and loose stools monitoring showed increased writhing and loose stools frequency of group 2, 3, 6 and 7 rabbits. However, treatment of paracetamol significantly reduced rectal temperature. Group 4 & 5 showed significant reduction of rectal temperature together with abatement of abdominal writhing and loose stools.

Conclusion: *N. vomica* ultra-high dilutions have normalized rectal temperature and prevented the abdominal writhing and loose stools in baker's yeast-induced fever model of rabbits. It could be due to antidotal activity of *N. vomica* ultra-high dilutions. Therefore, *N. vomica* ultra-high dilutions can be useful antipyretic agents and can treat conditions associated with gastrointestinal symptoms. However, fixed conclusion can't be asserted due to caveat of small sample size.

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1. Introduction

Fever is a complex response produced by infectious as well as non-infectious inflammatory conditions and is manifested primarily as elevated body temperature of about 1–4 °C [1]. Hyperthermia and fever may precipitate brain cell damage [2]. Antipyretic drugs such as aspirin, NSAIDs have been developed for use [3] but mostly produce side effects [4–6]. Hence, there is a need

for herbal medicines/homeopathic remedies with antipyretic effect and minimum/no side effect to be investigated.

Homeopathy is based on "*Similia similibus curantur*" which implies that treatment is done with something that is able to produce an effect similar to the suffering [7]. Homeopathy is a widely used but controversial alternative system of medicine [8]. The action of homeopathic medicines is considered slower. It is assumed that homeopathic medicines are ineffective in acute conditions such as fever. But anecdotal evidence indicated that various homeopathic medicines are being used for the treatment of fever. The old literature of homeopathy presents *Nux vomica* as an antidotal remedy for large doses of drugs, alcohol and foods [9]. Different researches

* Corresponding author.

E-mail address: tayyeba.rehman@yahoo.com (T. Rehman).

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substantiate the antidotal property of *N. vomica* ultra-high dilutions in alcohol intoxication [10–14]. In practice, *N. vomica* is used for various digestive disturbances and Crohn's disease [9]. Moreover, *N. vomica* is among the most frequently prescribed medicines in clinical practice of homeopathy [15].

Belladonna (*Bell*) is a homeopathic medicine for inflammation associated with heat [16]. *Bell* has reported actions viz antibacterial, anti-inflammatory, antiseptic, neurotropic and anti-protozoal [17–21]. In homeopathy, *Calcarea phosphoricum* is mostly used for bone problems [16].

Baker's yeast is commonly used in baking and brewing products [23]. In experimental animals, it induces fever with elevated plasma levels of IL-1b, interferon-c and TNF- α [24–26]. Various studies indicated baker's yeast fever induction to rabbits [27–29] and rats [24,26,30,31]. In current study, rabbits were selected as they develop fever more easily than rats [32]. Moreover, they have docile nature [33]. Baker's yeast is also a common dietary antigen and various antibodies against it are present in patients with Crohn's disease [23]. Crohn's disease may present with ileitis, ileocolitis diarrhea and fever accompanied with right lower quadrant pain [34].

In literature review, the antipyretic activity of ultra-high dilutions of *N. vomica*, *Bell* and *Calc. phos* against baker's yeast induced fever is not reported yet. The present experiments were therefore undertaken to find effects of *N. vomica* (remedy for gastric fever), *Bell* 200C (routine remedy for fever) and *Calc. phos* 200C (remedy has no relation to fever or digestive disturbances) against baker's yeast-induced fever. The secondary objective of study to see effects of all the medicines on gastric symptoms (diarrhea, abdominal writhing etc.).

2. Materials and methods

2.1. Drugs and chemicals

Paracetamol GlaxoSmithKline, Pakistan, Limited; *N. vomica* 1M & 200C, *Belladonna* 200C, *Calcarea phosphoricum* 200C (Dr. Willmar Schwabe GmbH & Co. KG, Germany); Baker's yeast (Rossmoor food products, Karachi, Pakistan); Ethanol (Merck, Germany); Succussed Alcohol 90% (Masood Homeopathic Pharmaceuticals, Pakistan); Normal Saline (Shazeb Pharmaceutical Industries Ltd); Flagyl-S 200 mg/5 ml Oral Suspension (SANOFI, Ireland).

2.2. Apparatus

Digital thermometer (Medisign MANA & CO Pakistan), Syringes (B.D Singapore).

2.3. Animals and housing conditions

Animals (male and female) used in this study were local strain rabbits (1.5–2 kg). Animals were housed in animal house of Khawaja Fareed Campus, Faculty of Pharmacy and Alternative Medicine, The Islamia University Bahawalpur. Before the start of the experiment, animals were acclimatized to animal house for seven days. Environmental conditions were maintained throughout the study period (12 h light/dark cycles, 23–25 °C and 50–55% humidity). They were provided with standard food and tap water *ad libitum*. They were fasted 24 h before the experiment but were given free access to water. The experiment complies with the declarations of Institute of Laboratory Animal Resources, Commission on Life Sciences [35]. The experimental protocol of current study was approved by Pharmacy Research Ethics Committee via notification number 88-2015/PREC. The manuscript complied with the ARRIVE guidelines [36].

2.4. Experimental design and procedure

In the current study, grouping of animals, drug administration, observations and analysis of results were conducted blind. Animals were divided into seven groups and each group contained 6 rabbits. Sample size was calculated by “resource equation” method [37]. All the rabbits were weighed and dosages of baker's yeast and paracetamol were adjusted according to each rabbit. Rectal temperature was monitored with a digital thermometer. Fever was induced according to the method of Tomazetti [26]. All the groups (except normal control) were treated with 135 mg/kg baker's yeast (*Saccharomyces cerevisiae*) suspension intraperitoneal for fever induction. Normal control group received normal saline intraperitoneal injection. Rectal temperature was checked after 4 h of intraperitoneal injection. 0.5–1.5 °C increase of temperature was considered as induced fever in rabbits [28]. After fever induction, the rabbits were given medicines according to their corresponding groups. Group 2 was negative control and it received 90% succussed alcohol mixed in 5 cc distilled water. Group 3 was standard control and it received paracetamol 150 mg/kg orally [28]. Groups 4 and 5 were given *N. vomica* 1M and 200 respectively. Groups 6 and 7 received *Calc. phos* 200C and *Bell* 200C respectively. All the homeopathic medicines and 90% succussed alcohol (vehicle used for homeopathic medicine as mentioned on purchased homeopathic potencies) were given orally in distilled water. For this purpose, 5 drops of each medicine were mixed in distilled water and 5 cc of this medicine containing distilled water was administered orally to rabbits of respective groups. *N. vomica* was administered orally in current study because a previous study showed its effects through oral receptors [10]. The other medicines were also given orally as the effect of route of administration of these medicines has not been evaluated previously. Moreover, minimum dose of ultra-high dilutions was administered to avoid medicinal aggravation. Rectal temperature was recorded hourly for 6 h after medicine administration. The animals were treated and assessed according to their group number mentioned (Fig. 1). Primary outcome was the assessment of temperature reduction that was checked with the help of digital thermometer. The secondary outcome measure was digestive symptoms that was assessed by appearance of loose stools.

2.5. Statistical analysis

Results of the current study were analyzed by IBM SPSS 20.0 software ([statistics.v20_32bit_oxava.com](http://www.ibm.com/software/development/it-infrastructure/ibm-spss-statistics/v20_32bit_oxava.com)). All the analyses were blinded. Temperature readings were expressed as Mean \pm Standard Error of Mean (S.E.M) of six readings. The test applied for analysis of data was Analysis of variance (ANOVA) followed by post hoc test. ANOVA for each time point was used for comparison between groups. Fischer LSD (Least significant difference) post hoc test was applied only if ANOVA was significant. For comparison of baseline data to follow up, Mann-Whitney U test was applied. $p \leq 0.05$ was taken as significant (Table 1).

3. Results

Baker's yeast administration caused fever in all the rabbits, as indicated by a drastic increase in temperature (Table 2). All the animals were returned to animal house for reuse in experiments.

3.1. Effect of normal saline intraperitoneal injection

As shown in Table 2, normal saline treatment caused no temperature variation in rabbits till the end of experiment.

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