In vivo evaluation of antipyretic effects of homoeopathic ultrahigh dilutions of *Typhoidinum* on baker's yeast-induced fever in comparison with *Paracetamol*

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Abstract

**Introduction:** Homoeopathy is a widely used, controversial alternative system of medicine. It is assumed that homoeopathic medicines are slower in action and does not work in acute conditions such as ‘fever’. The study aims to estimate the effectiveness of some homoeopathic remedies in fever and to compare their effects with *Paracetamol*. **Materials and Methods:** Baker’s yeast fever model of rabbits was used in the study. Rabbits were divided into four different groups (n = 6). Rectal temperature was measured before and after fever induction hourly. After fever induction, medicines were administered orally. *Paracetamol* and *Typhoidinum* in 200C and 1M potencies were given orally. ANOVA followed by post hoc test was used for statistical analysis of results. The results were considered statistically significant at *P* ≤ 0.05. **Results:** Fever was induced in all the rabbits after 4 h of baker’s yeast administration. The results of the study revealed the significant effectiveness of *Typhoidinum* in 200C and 1M potencies in baker’s yeast-induced fever (*P* = 0.05). *Typhoidinum* in both potencies showed less significant results as compared to *Paracetamol*. However, all the medicines’ effects were significant compared to the negative control. **Conclusion:** *Typhoidinum* 200C and 1M worked against baker’s yeast-induced fever. However, the results were slower and less significant than *Paracetamol* that might be due to lack of similarity of remedy picture and disease picture.

**Keywords:** Antipyretic, Homoeopathic ultrahigh dilutions, *Typhoidinum*

**INTRODUCTION**

Fever is a complex physiologic process that is characterised by elevated body temperature above the normal range, associated with increased pulse, aches, chills, tissue destructions, restlessness and other symptoms. Fever can be caused by many factors including factors effecting the temperature regulating centre, bacterial diseases, any abnormality in the brain as brain tumours and many environmental conditions such as heat stroke. The primary manifestation of fever is an elevation of body temperature, usually by 1°C–4°C. In fact, fever is not a disease, but it is the symptom of other pathological state and the immune response of the body that attempt to neutralise microbial infection in the body. Increased temperature led to the disturbance of the human physiology and is responsible for patient discomfort. There are various antipyretics to control fever such as *Paracetamol*. It reduces fever in multiple species including rabbits, but it has certain side effects, such as asthma, hepatotoxicity and hypertension. Thus, there is need to find therapeutic alternatives for fever.

Homoeopathy is one of the most popular complementary and alternative systems of medicine.

Homoeopathy is based on similia principle ‘similia similibus curantur’ that means to treat with something that can produce an effect similar to the suffering. Remedy pictures are obtained by administering homoeopathic medicines in non-toxic dilutions to healthy volunteers during homoeopathic drug proving. In Homoeopathy, medicines are selected based on the similarity between remedy picture and disease-specific individual status.

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Hahnemann often said that the primary method of treatment is to remove the fundamental cause of the disease.\cite{12}

*Typhoidinum* is a nosode (homeopathic remedy prepared from diseased products) prepared from *Salmonella typhi*. It is useful for fever with numbness all along right side, with impaired hearing in the right ear, slight nausea, vertigo and numbness that is worse from lying down and better in sitting position. General amelioration from lying down. There is no appetite and no thirst.\cite{13} *Typhoidinum* is proved to be antiviral medicine in one study. Homoeopathic medicines in potencies of 100C to 1M of *Typhoidinum*, *Tuberculinum*, *Hydrophobinum*, *Nux vomicida* and *Malandrinum* completely inhibit chicken embryo DNA virus-induced pock-like lesions. The effects were found to be significant compared to controls.\cite{14}

‘Baker’s yeast-induced fever model’ is a commonly used method of fever induction. In the experimental studies, baker’s yeast (*Saccharomyces cerevisiae*) causes fever in animals in large doses (intrapertoneally or subcutaneous).\cite{15,16} It causes high-grade fever in a very short period. Some studies have shown that *S. cerevisiae* and constituents of its cell wall, such as mannans, cause fever that is accompanied by an increase in the plasma levels of tumour necrosis factor-a, interleukin-1b and interferon-c.\cite{17,18}

The study aimed to evaluate:

1. The effectiveness of *Typhoidinum* (ultrahigh dilutions) in baker’s yeast-induced fever
2. The effectiveness of *Typhoidinum* (ultrahigh dilutions) in comparison with standard antipyretic ‘*Paracetamol*’.

**MATERIALS AND METHODS**

**Medicines, reagent and apparatus**

*Typhoidinum* 1M and 200C (Dr. Willmar Schwabe, GmbH and Co., KG, Germany), *Paracetamol* GlaxoSmithKline, Pakistan, Limited, baker yeast (Rossmoor food products, Karachi, Pakistan), Digital Thermometer (Medisign MANA and CO., Pakistan) were used.

**Animals**

Adult healthy rabbits of local strain were purchased from the market. The weight of rabbits ranged from 1 to 1.5 kg, and both male and female rabbits were included in the study. The study was carried in rabbits as they are not aggressive and comes under the purview of local Ethical Committee.\cite{19} Moreover, rabbits were selected because they develop fever more easily than rats.\cite{20}

All the animals stayed in the air-conditioned animal house situated in Khawaja Fareed Campus, in the Faculty of Pharmacy and Alternative Medicine, the Islamia University of Bahawalpur Figure 1. They were fed on standard diet *ad libitum*. They were acclimatised to animal house conditions 7 days before the start of the experiment. They were also habituated to handling, temperature measurement procedure and injection stress. The study was approved by the Pharmacy Research Ethics Committee, Faculty of Pharmacy and Alternative Medicine, the Islamia University of Bahawalpur, Pakistan, through Notification number ‘88-2015/PREC’.

**Antipyretic activity**

Animals were grouped into four groups and each group contained six rabbits. The dosage of baker’s yeast as well as *Paracetamol* was adjusted according to weight of each rabbit. Rectal temperature of rabbits was checked with digital thermometer. Fever-inducing agent was prepared according to method of Tomazetti et al.\cite{15} Commercially available baker’s yeast (*S. cerevisiae*) was suspended in normal saline and was injected intraperitoneally at the dosage of 135 mg/kg/10 ml to induce fever. Rectal temperature was checked after 4 h of yeast injection.\cite{15} Temperature raise ≥0.5°F–1.5°F was considered as ‘induced fever’. Group I was negative control and received 90% succussed alcohol (vehicle of used homeopathic medicines). Group 2 was standard control and received *Paracetamol* 150 mg/kg orally.\cite{16} Groups 3 and 4 received *Typhoidinum* 1M and 200C, respectively. A few drops of homeopathic medicines in 5 cc distilled water were administered orally to rabbits of respective groups. Minimum dose of ultrahigh dilutions was administered to avoid medicinal aggravation. Negative control group received few drops of succussed alcohol in 5 cc distilled water orally. Rectal temperature of rabbits was again checked after administration of medicines hourly.

**Statistical analysis**

Results obtained by this activity were analysed by Social package of Statistical sciences SPSS version 20.0 software. The test applied for analysis of data was ANOVA followed by post hoc test. ANOVA was used for comparison among groups. Fischer least significant difference post hoc test was applied only if ANOVA was significant. *P* ≤ 0.05 was taken as statistically significant.

**RESULTS**

At the 4th h after yeast administration, temperature of more than 1°F was raised in all the rabbits. The temperature variations in different groups at different hours are as follows.

**Figure 1:** Rabbits in animal house of Khawaja Fareed Campus
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Effect of vehicle on fever induced by baker’s yeast
The negative control group showed a continuous increase of temperature till the 8th h from the time of yeast administration and then showed the progressive decline in temperature. At 0 h, normal mean temperature of the group was 102.6°F. Up till 8th h, a temperature raise of 2.3°F was observed that is started to decline afterward [Figure 2]. Three of the rabbits in negative control group suffered from diarrhoea (greenish watery) and later euthanised in the end of 5th h.

Effect of Paracetamol on fever induced by baker’s yeast
At 4th h of yeast administration, 2.8°F temperature increase was observed. Paracetamol was administered orally at this time, and this group showed the decrease of 2°F temperature in the 1st h of medicine administration (P = 0.002). At the 2nd h of medicine administration, a further decrease of 0.2°F temperature was observed (P < 0.001). In the succeeding 2 h, a slight increase of temperature was seen that was going to normal temperature in the 10th h of the experiment [Figures 2-5]. All the rabbits survived in this group.

Effect of Typhoidinum 1M on fever induced by baker’s yeast
Typhoidinum 1M group showed an increase of 3°F after 4 h of yeast administration. After medicine administration, a gradual decrease of temperature was observed that became statistically significant (P < 0.05) in 3rd h to onward [Figure 2]. At the end of experiment, both Paracetamol and Typhoidinum 1M showed equal decrease of temperature (P < 0.001) [Figure 3].

Effect of Typhoidinum 200C on fever induced by baker’s yeast
Typhoidinum 200C group showed an increase of 2.2°F after 4 h of yeast administration. After medicine administration, a slight non-significant decrease of temperature was observed in first 2 h. In 3rd h temperature decrease became significant (P < 0.05) that was continuous at the end of experiment [Figure 4]. At the end of experiment, both Paracetamol and Typhoidinum 200C showed equal decrease of temperature (P < 0.001) [Figure 5].

DISCUSSION
Homoeopathy is the widely used complementary and alternative system of medicine.[9] Homoeopathy faces many criticisms, the most common condemnation is about biological activities of homoeopathic ultrahigh dilutions beyond
Avogadro’s number.[21] The present study examined the effects of Typhoidinum in fever in baker’s yeast-induced fever model of rabbits. In the present study, administration of baker’s yeast in rabbits causes a significant elevation of temperature in 4 h. Our results matched to earlier studies reporting fever induced by baker’s yeast in rats and rabbits.[15,22]

Orally administered Paracetamol (150 mg/kg) significantly decreased baker’s yeast-induced fever in rabbits. Results are in accordance with other study results.[16,23,24] Typhoidinum ultrahigh dilutions slowly decreased temperature as compared to Paracetamol; however, results became statistically significant in 3rd h of medicine administration. Antipyritics and non-steroidal anti-inflammatory drugs decreased fever by decreasing inflammation at the peripheral sites in tissue inflammation and within central nervous system thermoregulatory sites.[25] However, homeopathic medicines has supposed action on the regulation of inflammatory pathological changes as it is perceived as an expression of natural healing dynamics (commonly known as Hahnemann’s ‘life force’).[26] Homeopathic medicines in ultra-high dilutions are safe and have no adverse effects.[27] Large doses of ultrahigh dilutions ingestion showed that nothing happened, they have not the power to cause adverse effects as the conventional drugs.[28]

In Homoeopathy, medicines are selected based on the similarity between drug-specific pathogenesis ‘remedy picture’ and disease-specific individual status.[11] Typhoidinum is useful for low-grade fever types such as typhoid with numbness.[13] Baker’s yeast caused high-grade fever during the study. Lack of complete similarity between disease condition and remedy picture might be responsible for slow onset of decline in temperature by Typhoidinum ultrahigh dilutions as compared to Paracetamol. Another study with similar protocols reported effectiveness of Aconitum napellus on baker’s yeast-induced fever due to similarity of high-grade fever.[21]

The potency should be selected according to disease energy activity (intensity), intense diseases need higher and mild diseases require lower or medium potency.[29] Experimentally induced diseases are short term and high intensity.[13] It is evident from study results that both selected potencies (high potencies of Typhoidinum) have similar effect in reducing temperature.

The specific effects of homoeopathic medicines are of a non-molecular origin, yet provide powerful biological activities that are clinically effective.[20] It has been assumed that highly diluted substances transfer biological activity to cells by electromagnetic fields. Another working hypothesis about homoeopathic ultrahigh dilutions is interactions between the radiation fields of a charged molecule. The electric dipoles of water generate permanent polarisation of water which becomes coherent. It transmits specific information to cell receptors, somewhat like a laser.[50] However, the exact mechanism of action of homoeopathic ultrahigh dilution is not proved yet.

The effects of Typhoidinum ultrahigh dilutions should be evaluated on S. typhi-induced fever as it is the source of medicine administration. It can be hypothesised that medicine will be more effectively work in S. typhi-induced fever. Moreover, it can also be hypothesised that Belladonna and Pyrogenium would be effective remedies in baker’s yeast-induced fever on the basis of some similarity of these medicines with baker’s yeast-induced fever.

**Conclusion**

Homoeopathic medicines worked well when the criteria of similarity met entirely. If disease picture and drug picture have partial similarity, then results are slower or sometimes none. However, there is no ambiguity about the effects of homeopathic medicines as the study showed positive results on animals. Hence, the effects of homoeopathic medicines are not mere placebos, and in fever, homoeopathic medicines worked as Paracetamol.

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**Conflicts of interest**

None declared.

**References**

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In Vivo Bewertung Antipyretischer Wirkung Von Homoeopathischen Ul-Trahohen Typhoidinum Verdünnungen Bei Bäckerhefeindiziertem Fieber Im Vergleich Zu Paracetamol

Abstrakt


Fazit: Typhoidinum C 200 und 1 M wirken gegen von Bäckerhefe induziertes Fieber. Aber die Ergebnisse stellten sich langsamer und weniger signifikant als bei Paracetamol ein, was an einer mangelnden Ähnlichkeitsbeziehung von und Arzneimittel- und Krankheitsbild gelegen haben dürfte.

Evalúación In Vivo de Los Efectos Antipiréticos De Las Ultradiluciones Homeopáticas De Typhoidinum En La Fiebre Inducida Por La Levadura Del Pan, En Comparación Con El Paracetamol

Resumen

Introducción: La homeopatía, un sistema médico alternativo controvertido, se utiliza ampliamente. Se supone que los medicamentos homeopáticos tienen una acción más lenta y no funcionan en patologías agudas como la “fiebre”. El objetivo del estudio es estimar la eficacia de algunos remedios homeopáticos en la fiebre y comparar sus efectos con el paracetamol.

Métodos: En este estudio en conejos, se aplicó el modelo de fiebre por la levadura del pan. Los conejos fueron divididos en 4 grupos diferentes (n=6). La temperatura rectal se midió cada hora antes y después de la inducción de la fiebre. Tras la inducción de la fiebre, los medicamentos, paracetamol y Typhoidinum (potencias: 200c y 1M), se administraron por vía oral. Se utilizó ANOVA seguido de una prueba post-hoc para el análisis estadístico de los resultados. Los resultados fueron considerados significativos a p ≤ 0,05.

Resultados: En todos los conejos se indujo fiebre cuatro horas tras la administración de la levadura del pan. Los resultados del estudio revelan una eficacia significativa de Typhoidinum las potencias de 200c y 1M en la fiebre inducida por la levadura del pan(P 0,05). Las dos potencias de Typhoidinum dieron lugar a resultados menos significativos en comparación con el paracetamol. Sin embargo, todos los efectos medicamentosos fueron significativos en comparación el control negativo.

Conclusiones: Typhoidinum 200c y 1M fueron eficaces en la fiebre inducida por la levadura del pan. Sin embargo, los resultados fueron más lentos y menos significativos que el paracetamol, lo que puede deberse a la falta de similitud del cuadro del medicamento con el cuadro patológico.
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Une évaluation in vivo des effets antipyrétiques des dilutions homéopathiques ultra-élevées du Typhoidinum dans le cas de la fièvre induite par la levure de boulanger par rapport au Paracétamol

Résumé

Introduction: L'homéopathie est un système de médecine alternative largement utilisé et controversé. On suppose que les médicaments homéopathiques ont une action plus lente et ne sont pas efficaces dans des conditions aiguës comme 'la fièvre'. L'étude vise à estimer l'efficacité de certains remèdes homéopathiques dans le cas de la fièvre et à comparer leurs effets à ceux du Paracétamol. Matériels et Méthodes: Le modèle des lapins atteints de la fièvre induite par la levure de boulanger a été utilisé dans l'étude. Les lapins ont été répartis sur quatre groupes différents (n=6). La température rectale a été mesurée toutes les heures avant et après l'induction de la fièvre. Après l'induction de la fièvre, les médicaments ont été administrés par voie orale. Le Paracétamol et le Typhoidinum dans des potences de 200c et 1M ont été administrés par voie orale. L'analyse de la variance (ANOVA) suivie d'un test post hoc a été utilisée pour faire une analyse statistique des résultats. Les résultats ont été considérés comme étant statistiquement significatifs à P ≤ 0.05. Résultats: La fièvre a été induite chez tous les lapins 4 heures après l’administration de la levure de boulanger. Les résultats de l’étude ont révélé l’efficacité significative du Typhoidinum dans des potences de 200c et 1M dans le cas de la fièvre induite par la levure de boulanger (P = 0.05). Le Typhoidinum dans les deux potences a montré des résultats moins significatifs par rapport au Paracétamol. Cependant, les effets de tous les médicaments étaient significatifs par rapport au contrôle négatif. Conclusion: Le Typhoidinum à 200c et à 1M s’est avéré efficace contre la fièvre induite par la levure de boulanger. Cependant, les résultats ont été plus lents et moins significatifs que ceux obtenus avec le Paracétamol, ce qui pourrait être dû au manque de similitude quant à la présentation du remède et à celle de la maladie.