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Assessing the Impact of Postural Restriction on the Pharmacokinetics of Mebendazole in Healthy volunteers

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KEYWORDS

Postural Restriction, Pharmacokinetics

ABSTRACT:

Introduction: Mebendazole, a BCS Class II drug, demonstrates poor aqueous solubility and variable systemic absorption. While the impact of food on its pharmacokinetics is well established, the influence of postural restriction on its absorption remains unclear.

Objectives

To evaluate whether maintaining a seated, upright posture after dosing alters the pharmacokinetics of mebendazole administered under fed conditions in healthy volunteers.

Methods: A randomised, open-label, two-period crossover study was conducted in 24 healthy volunteers. Each subject received a single 500 mg dose of mebendazole under fed conditions, either with four hours of seated postural restriction or without any restriction. Plasma concentrations were quantified using a validated LC-MS/MS method. Pharmacokinetic parameters including C_{max}, AUC_{0-t}, T_{max}, t½, and Kel were calculated and compared using the Wilcoxon signed-rank test.

Results: Postural restriction showed a non-significant trend towards higher C_{max} (79.35 ± 55.17 vs. 73.30 ± 39.70 ng/mL; p=0.603) and AUC_{0-t} (480.92 ± 72.67 vs. 465.95 ± 73.73 ng·h/mL; p=0.900). T_{max}, t½, and Kel was comparable across conditions. The findings suggest that posture exerts minimal influence on mebendazole pharmacokinetics under fed conditions.

Conclusions:

Postural restriction has limited impact on mebendazole pharmacokinetics. Clinical emphasis should remain on dietary factors, particularly co-administration with high-fat meals, rather than postural adjustments.

1. Introduction

Mebendazole, a broad-spectrum anthelmintic, is widely used for treating parasitic infections. It has also been utilized for the medical treatment of alveolar and cystic hydatid diseases [1, 2], where it aims to inhibit the growth and spread of the parasitic cysts, particularly in inoperable cases or as an adjunct to surgery. It is classified as a Biopharmaceutics Classification System (BCS) Class II drug, characterized by low aqueous solubility and high permeability [3,4]. Due to its poor solubility, mebendazole's systemic exposure is primarily dissolution-limited; thus, co-administration with high-fat meals is recommended to enhance its bioavailability. Due to its poor solubility, mebendazole's systemic exposure is primarily dissolution-limited; thus, co-administration with high-fat meals is recommended to improve its bioavailability. [1,5] High-fat meals are known to enhance its bioavailability by stimulating bile secretion, thereby promoting drug solubilization and absorption in the gastrointestinal (GI) tract [6]. While the effects of food and bile salts on mebendazole absorption are well-documented, the influence of posture on its pharmacokinetics remains underexplored.[7]. Queckenberg et al (2009) [7] reported that sitting, standing, or lying on right side accelerate gastric emptying compared to supine position, which may lead to variations in drug dissolution rates and absorption kinetics for orally administered drugs [8]. Conversely, lying down or adopting a recumbent posture may prolong gastric retention time, potentially leading to delayed but more complete dissolution of poorly soluble drugs like mebendazole [7,8].

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Considering the known fact that mebendazole's absorption is already constrained by its poor solubility, any factor that modulates gastrointestinal transit could contribute to interindividual variability in drug exposure. However, compared to the pronounced effect of food, the impact of posture on mebendazole pharmacokinetics needs investigation. Therefore, this study aimed to evaluate whether maintaining a seated, upright posture after dosing alters the pharmacokinetics of mebendazole administered under fed conditions in healthy volunteers.

2. Materials and Methods

Study Design

The present study was a randomized, open-label, single-dose, two-period, two-sequence crossover study conducted in healthy volunteers to assess the impact of postural restriction on the pharmacokinetic profiles of Mebendazole Chewable Tablets (500 mg) under fed conditions. The crossover design allowed each participant to serve as their own control, thereby minimising interindividual variability.

Study Participants

A total of 24 healthy volunteers satisfying the inclusion and exclusion criteria were enrolled in the study. All study participants provided written informed consent prior to the enrolment. The study was conducted following approval from the Naithika Independent Ethics Committee, Hyderabad (Protocol No. 116/21-22).

Inclusion Criteria

All study participants who provided written informed consent and were healthy adult males or non-pregnant, non-lactating females aged 18–45 years were included in the study. They had a BMI between 18.5 kg/m² and 30 kg/m², with a minimum body weight of 55 kg. Only non-smokers and non-alcoholics with normal blood pressure and vital signs were included. Participants with normal health status as determined by medical history and physical examination, along with normal ECG and chest X-ray findings were included in the study. Additionally, they were required to be available for the entire study duration. Female participants of childbearing potential were required to use an acceptable contraceptive method during the study.

Exclusion Criteria

Study participants were excluded from the study if they could not understand or provide informed consent, or had known hypersensitivity to the study drug or related compounds, or showed evidence of organ dysfunction. Those who had taken prescription or over-the-counter medications within 30 days prior to screening (unless permitted by the protocol) or had a history of psychiatric illness that could interfere with study compliance were also excluded. Participants with abnormal laboratory parameters, recent participation in clinical trials within the past three months, or an inability to comply with the study protocol were not eligible. Additional exclusions included contraindications for the study drug, intolerance to venipuncture, and positive tests for drugs of abuse or pregnancy. Female participants who had recently used hormonal contraceptives or were breastfeeding were also excluded.

Study Drug and Administration

The study drug Mebendazole Chewable Tablets 500 mg was procured from Pharmazone, Ahmedabad. Participants received a single 500 mg dose of mebendazole post-meal. In one period, participants were instructed to remain seated upright for four hours post-dose, while in the other period, they were allowed to adopt unrestricted postures.

Pharmacokinetic Sampling

A total of 25 blood samples, each of 03 mL were collected from each participant. The venous blood samples were withdrawn at pre-dose (0.000 hour) and after dosing at 00.50, 01.00, 01.50, 02.00, 02.33, 02.67, 03.00, 03.33, 03.67, 04.00, 04.33, 04.67, 05.00, 05.33, 05.67, 06.00, 06.50, 07.00, 08.00, 10.00, 12.00, 18.00, 24.00 and 32.00 hrs were collected.

Bioanalytical Methods

Mebendazole concentrations in plasma were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method developed by Vimta Labs Ltd., Hyderabad.

Statistical Analysis

The sample size of 24 participants was selected based on feasibility and prior studies assessing postural effects on pharmacokinetics. A formal power calculation was not

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conducted; however, the study aimed to detect a moderate effect size (Cohen's d = 0.5) with 80% power at a significance level of 0.05. Primary pharmacokinetic parameters assessed were C_{max} and AUC_{0-t}. Secondary parameters included AUC_{0-inf}, T_{max}, elimination half-life (t½), and elimination rate constant (Kel). All data were expressed as mean ± SEM. The Wilcoxon signed-rank test (two-tailed) was used for within-subject comparisons of pharmacokinetic parameters between postural conditions. A p-value <0.05 was considered statistically significant. Data analysis was performed using SAS software version 9.4 (SAS Institute, USA).

Ethical Considerations

The study adhered to the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. Written informed consent was obtained from all participants before any study procedures were initiated. The study was approved by the Naithika Independent Ethics Committee, Hyderabad (Protocol No. 116/21-22).

3. Results

Pharmacokinetic data for mebendazole under postural restriction (seated for four hours post-dose) and unrestricted posture are presented in Table 1.

Effect of Postural Restrictions on Pharmacokinetic Parameters

Maximum Plasma Concentration (C_{max})

The mean plasma concentration-time profiles of mebendazole under both postural conditions are presented in Figures 1 and 2.

C_{max} values as depicted in Table 1, for the test formulation exhibited slightly higher peak plasma concentrations under postural restriction (79.35 ± 55.17 ng/ml) compared to non-restricted condition (73.30 ± 39.70 ng/ml). Although the difference was not substantial, it was also statistically insignificant (p=0.603).

T_{max}

T_{max} showed a slight delay under postural restriction (4.08 ± 0.44 h) compared to unrestricted posture (3.75 ± 0.43 h), but this difference was not significant (p = 0.336).

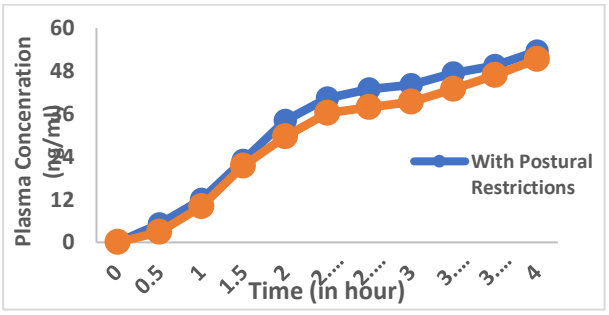

Figure 1:Mean plasma concentrations of Mebendazole during first 4 hours

Area Under Curve (AUC)

For total drug exposure, the AUC_{0-t} values for the test formulation were 480.92 ± 72.67 ng·h/mL with postural restriction and 465.95 ± 73.73 ng·h/mL without restriction. Similarly, the AUC_{0-inf} values followed the same trend, with the test formulation showing 519.30 ± 76.81 ng·h/mL under postural restriction and 504.28 ± 80.23 ng·h/mL without. These results suggest that postural restriction led to slightly higher systemic exposure to mebendazole, although the differences were not statistically significant (p = 0.900 and p = 0.944, respectively). Figure 2

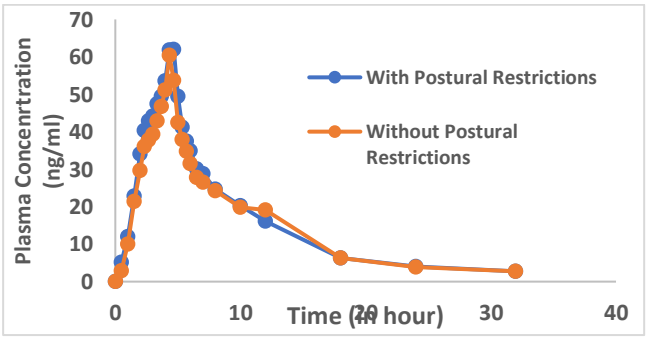

Figure 2: Mean plasma concentrations of mebendazole with and without postural restrictions

Elimination Half-Life(t½) and Elimination Rate Constant (Kel)

The half-life (t½) was comparable between conditions for the test formulation (T1: 9.18 ± 0.96 h vs. T2: 8.92 ± 0.93 h, p = 0.584). The elimination rate constant (Kel) remained stable across both conditions for the test formulation (T1: 0.09 ± 0.04 h^{-1} vs. T2: 0.09 ± 0.04 h^{-1}, p=0.663), suggesting that postural changes did not significantly affect elimination kinetics.

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Discussion

Posture is a physiological factor known to influence gastrointestinal (GI) motility and gastric emptying, both of which play critical roles in the dissolution and absorption of orally administered drugs [7,9]. Mebendazole, a benzimidazole anthelmintic agent, belongs to the Biopharmaceutics Classification System (BCS) Class II, characterised by low aqueous solubility and high permeability [2,4,6]. Its systemic absorption is dissolution-limited, making it sensitive to gastrointestinal conditions such as motility, gastric residence time, and fed or fasted states [1,3].

In this study, we investigated whether maintaining a seated, upright posture for four hours post-dose could influence the pharmacokinetics of mebendazole when administered under fed conditions. Our findings demonstrate only a modest and statistically non-significant effect of posture on mebendazole absorption. A slight increase in C_{max} (79.35 ± 55.17 ng/mL vs. 73.30 ± 39.70 ng/mL) and a minor delay in T_{max} (4.08 ± 0.44 h vs. 3.75 ± 0.43 h) were observed under postural restriction. Similarly, both AUC_{0-t} and AUC_{0-inf} trended slightly higher, suggesting a marginal increase in systemic exposure. However, these differences were not statistically significant ($p > 0.05$), indicating that posture alone does not have a clinically meaningful impact on mebendazole pharmacokinetics [3,9,10].

The modest pharmacokinetic changes observed in this study align with prior findings that suggest posture can influence gastric emptying and GI transit. Upright positions typically accelerate gastric emptying compared to supine or recumbent postures, potentially affecting drug dissolution and absorption [7,8,11]. However, such effects appear to be secondary in comparison to dietary factors. Notably, high-fat meals have been consistently shown to enhance the absorption of poorly soluble drugs like mebendazole by stimulating bile secretion, promoting micellar solubilisation, and inducing supersaturation in the intestinal lumen [5,6,12,13,14].

In our study, the presence of a high-fat meal likely masked any minor influence posture may have had on gastric emptying. The observed delay in T_{max} under postural restriction could reflect prolonged gastric residence time, enabling more complete dissolution of mebendazole. This supports earlier observations that food delays gastric emptying and alters drug absorption kinetics [10,12,13].

Moreover, computational and physiologically based pharmacokinetic models have illustrated that posture-related changes in gastric geometry and fluid distribution can impact dissolution and bioavailability [8,15]. These theoretical models provide a mechanistic understanding of posture-dependent drug absorption, although their clinical impact appears minimal in the presence of a high-fat meal. Mebendazole's pharmacological activity is predominantly localised within the GI tract for treating intestinal helminthic infections, making systemic bioavailability less critical in most clinical applications [1,2,4]. For systemic indications, such as echinococcosis and neurocysticercosis, higher systemic exposure becomes more relevant [16,17]. In such cases, co-administration with high-fat meals, rather than postural adjustments, is a more effective strategy to enhance bioavailability [5,13,14].

Our study has limitations. Although the sample size was comparable to other pharmacokinetic studies [3,9], it may not have been powered sufficiently to detect small but potentially meaningful differences. Additionally, the study was conducted in healthy adult volunteers under fed conditions, which may limit extrapolation to patient populations with altered GI physiology or under fasting conditions. The fasting state exhibits markedly different gastric emptying kinetics and reduced bile secretion, potentially magnifying posture-related effects [11,15].

Future research could explore the influence of posture on pharmacokinetics under fasting conditions and in patients with GI motility disorders or those taking drugs with narrow therapeutic windows. Additionally, posture has been implicated in hepatic blood flow and presystemic drug metabolism, which could influence systemic bioavailability for drugs with extensive first-pass metabolism [18-19].

In conclusion, this study demonstrates that postural restriction has a minor and statistically non-significant effect on mebendazole pharmacokinetics under fed conditions. The role of posture in modulating drug absorption for BCS Class II drugs appears limited, especially in the presence of high-fat meals, which exert a more substantial influence on bioavailability. Clinical recommendations should continue to emphasize dietary factors over postural modifications for optimizing mebendazole absorption.

Conflict of Interest

The authors declare no conflict of interest.

Informed consent

All participants provided written informed consent before the experiment.

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