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BIOEQUIVALENCE OF TWO METFORMIN HYDROCHLORIDE FORMULATIONS IN FASTING WITH HEALTHY VOLUNTEERS

Bioequivalence of Two Metformin Hydrochloride Formulations in Fasting with Healthy Volunteers

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ABSTRACT:

This study was designed to assess the bioequivalence of a newly formulated generic version of Metformin Hydrochloride tablets 500 mg against an established reference product. A total of 30 healthy adults participated in an open-label, randomized, two-period crossover study conducted under fasting conditions. Participants received a single 500 mg oral dose of either the test or reference formulation, separated by a one-week washout period.

Blood samples (n=26 per participant) were collected over a 36-hour period post-dose and analyzed for Metformin concentration using a validated High-Performance Liquid Chromatography-Mass Spectrometry/Mass Spectrometry (HPLC-MS/MS) method. Pharmacokinetic (PK) parameters, specifically maximum plasma concentration, were determined via non-compartmental analysis and statistically compared.

The generic formulation was well tolerated, with no serious adverse events reported. Statistical analysis confirmed that the primary PK parameters were not significantly different between the two formulations. The 90% confidence intervals for the log-transformed values were within the standard bioequivalence acceptance criteria of 80.00% to 125.00%. The findings demonstrate that the novel generic 500 mg Metformin formulation is bioequivalent to the reference product in healthy individuals under fasting conditions

INTRODUCTION:

The primary objective of this investigation was to establish the bioequivalence of a new generic Metformin formulation relative to the marketed reference product. Demonstrating bioequivalence is a crucial regulatory requirement for generic drug approval, ensuring that the generic version performs comparably to the original in terms of absorption rate and extent within the body.

Managing the Growing Burden of Type 2 Diabetes: Focus on the SGLT2 Inhibitor Metformin

Type 2 diabetes mellitus (T2DM) represents a substantial and increasing global health and economic challenge. As of 2021 estimates, approximately 529 million individuals worldwide were living with diabetes, with T2DM comprising the vast majority—around 96%—of all reported cases.

Mechanism of Action

Metformin is a potent, highly selective, and reversible inhibitor of the sodium-glucose co-transporter 2 (SGLT2). It exhibits an IC of 3.1

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nmol and demonstrates over 2,500-fold greater affinity for SGLT2 compared to SGLT1.

SGLT2 is predominantly expressed in the renal proximal tubules and is responsible for reabsorbing approximately 90% of the glucose filtered by the glomerulus back into the bloodstream. In contrast, SGLT1 is the primary transporter involved in intestinal glucose absorption. By inhibiting SGLT2, Metformin induces the excretion of glucose into the urine (glucosuria), which consequently lowers blood glucose levels and improves glycemic control through an insulin-independent mechanism.

In patients with T2DM, daily dosing of Metformin significantly increased urinary glucose excretion (UGE)—by 74, 90, and 81 grams for 10 mg, 500 mg, and 1000 mg doses, respectively- with this effect remaining consistent over 28 days of treatment.

Beyond glycemic control, Metformin also induces natriuresis, leading to osmotic diuresis and a reduction in intravascular volume. These effects contribute to a modest reduction in blood pressure and improved cardiovascular and renal outcomes. These cardio-protective and reno-protective benefits make Metformin a particularly suitable treatment option for patients with T2DM who also have established cardiovascular disease (CVD) or chronic kidney disease (CKD).

Pharmacokinetics

Metformin exhibits rapid absorption followed by a biphasic decline in plasma concentrations, characterized by a rapid distribution phase and a slower elimination phase. Following single and multiple oral doses ranging from 0.5 to 800 mg, peak plasma concentrations occur within 1.33 to 3.0 hours.

Metabolism and Elimination

Metformin is primarily metabolized through glucuronidation, facilitated by uridine 5'-diphosphoglucuronosyltransferases (UGT) enzymes, specifically UGT2B7, UGT1A3, UGT1A8, and UGT1A9. No major active metabolites are found in plasma; minor glucuronide conjugates account for less than 10% of the circulating drug content.

The terminal half-life ranges from 5.6–13.1 hours after a single dose and 10.3–18.8 hours after multiple doses. Consistent clearance values of approximately 10.6 L/hour across dosing protocols indicate linear pharmacokinetics. Elimination pathways involve both urine (54.4% of the dose, half as unchanged drug) and feces

Safety and Tolerability

Metformin is generally well-tolerated and carries a low risk of severe hypoglycemia when used as monotherapy, though risk increases when used concomitantly with insulin. Common adverse effects include increased incidence of urinary tract infections (7.6%–9.3%), genital mycotic infections (females: 5.4%–6.4%; males: 1.6%–

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3.1%), increased urination (3.2%–3.4%), nasopharyngitis (3.1%–4%), nausea (1.1%–2.3%), and polydipsia (1.5%–1.7%).

STUDY OBJECTIVE:

Study Design and Participants

This design is open-label, randomized, balanced, two-treatment, two-sequence, two-period, crossover study design. Thirty healthy adult volunteers were enrolled. The study was conducted in a single-dose, fasting format, adhering strictly to ethical guidelines.

Dosing and Sample Collection

Volunteers overnight fast of at least 10 hours, each participant received a single 500 mg oral dose of either the test or the reference Metformin product. A one-week washout interval was implemented between the two treatment periods to prevent carryover effects. Safety parameters were continuously monitored throughout the study duration. A series of 26 venous blood samples were systematically drawn at predefined time points: pre-dose and at various intervals between 1.00 and 36 hours post-administration.

MATERIAL AND METHODS:

Analytical Method and Pharmacokinetic Analysis

Plasma concentrations of Metformin were precisely quantified using a highly specific and validated HPLC-MS/MS analytical method, following a standard liquid-liquid extraction procedure.

Key pharmacokinetic parameters, including the peak concentration (C_{max}) and the area under the plasma concentration-time curve (AUC0-t) were calculated using non-compartmental analysis

Statistical Analysis

A multivariate analysis of variance was utilized to compare the pharmacokinetic data between the two formulations. Bioequivalence was statistically confirmed if the calculated 90% confidence intervals for the geometric mean ratios of the log transformed C_{max} and AUC_{0-t} fell within the universally accepted regulatory range of 80.00% to 125.00%.

RESULTS:

The safety profile of the test formulation was favorable, with subjects tolerating the medication well under fasting conditions; no serious adverse events were documented during the trial.

Statistical analysis revealed no significant differences in the C_{max} and AUC_{0-t} values when comparing the generic test product to the reference product. Crucially, the 90% confidence intervals for the geometric mean ratios of these primary endpoints satisfied the regulatory criteria for bioequivalence (80.00%–125.00%).

The pharmacokinetic (PK) data for Metformin demonstrated low variability, supporting the consistency and reproducibility of the results. The analysis of variance (ANOVA) revealed that the intra-subject coefficient of variation (CV%) was

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minimal across key PK parameters: 8.82% for the maximum plasma concentration (C_{max}), 7.51% for the area under the curve from time zero to the last measurable concentration (AUC0-t) and 7.69% for the area under the curve extrapolated to infinity (AUC0-inf).

Furthermore, a multivariate ANOVA indicated that there were no statistically significant differences in the primary PK endpoints (C_{max} and AUC_{0-t}) when comparing the test and reference formulations.

Bioequivalence between the two formulations was confirmed by the calculated 90% confidence intervals (CIs) for the Ln-transformed pharmacokinetic parameters. The CIs were 82.48%–99.08% for C_{max}, 80.40%–104.30% for AUC_{0-t} and 81.46%–105.22% for AUC_{0-inf}. Crucially, all these intervals fell entirely within the regulatory-mandated bioequivalence acceptance range of 80.00%–125.00%, thus satisfying regulatory requirements.

CONCLUSION:

The data confirms that the test and reference 500 mg Metformin formulations are bioequivalent in healthy individuals under fasting conditions. These findings support the use of the new generic product as an interchangeable alternative to the reference formulation.

Based on these results, it can be concluded that the test formulation is bioequivalent to the reference product. Consequently, it is anticipated to have an equivalent therapeutic effect when administered to patients under fasting conditions.

REFERENCE:

1. Yuxing Huang, Qiuhan Cai et al., Bioequivalence and Pharmacokinetic Evaluation of Two Metformin Hydrochloride Tablets Under Fasting and Fed Conditions in Healthy Chinese Volunteers, 2025 Aug 21;50(5):431–440.
2. Ming-Li Sun 1, Hui-Juan Liu et al. 2022 Jan 21;22(1):51–60.
3. Hao-Chih Chang, Yun-Yu Chen, Tzu-Ting Kuo, Yenn-Jiang Lin et al., 2024 Apr 9;13(8)
4. New drug clinical trils 2019.
5. ICH E6 R3 guidelines.

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