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CLINICAL TRIAL REPORT

High-Fat Meal Increase Blonanserin Bioavailability 5-Fold in Chinese Healthy Subjects

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Purpose: Although blonanserin is widely used in clinical practice, existing studies have shown significant variations in the magnitude of food effects on its pharmacokinetics. This study was conducted to evaluate the impact of food on the pharmacokinetics and safety of 4-mg blonanserin tablets in healthy Chinese subjects.

Methods: The findings were derived from a bioequivalence study in which subjects were randomly assigned to receive blonanserin tablets under fasting or fed conditions. Serial blood samples were collected and plasma concentrations of blonanserin were accurately determined using a validated high-performance liquid chromatography-mass spectrometry (HPLC-MS/MS). Pharmacokinetic parameters, including the maximum plasma concentration (C_{max}), the area under the concentration-time curve from zero to the last quantifiable time point ($AUC_{0\text{-}t}$), and the area under the concentration-time curve from zero to infinity ($AUC_{0\text{-}\infty}$) were estimated using the non-compartmental method and statistically analyzed by the BE module of WinNonLin. Safety assessments were performed throughout the study period.

Results: 106 healthy subjects were enrolled and divided into a fasted group and a fed group. The C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of blonanserin in plasma after a high-fat meal increased 5.23-fold, 4.77-fold and 4.82-fold, relative to the fasted conditions. The 90% confidence interval (90% CI) were outside the 80.00–125.00% range. The incidence of adverse drug reaction (ADR) was similar between the fasted group and the fed group, with the majority being mild in severity.

Conclusion: The results revealed that a high-fat meal significantly increased blonanserin bioavailability by approximately 5-fold at the 4-mg dose. Blonanserin was well tolerated in most subjects under both fasting and fed conditions, and food intake did not significantly alter its safety profile. These findings highlight the need to consider food effects when determining clinical dosing regimens.

Keywords: blonanserin, high-fat meal, pharmacokinetics, safety

Introduction

Schizophrenia is a psychiatric disorder that typically emerges during late adolescence or early adulthood. It is characterized by positive symptoms including hallucination or delusion, negative symptoms such as apathy or avolition, and cognitive dysfunction.[1] Over the past few decades, the incidence of schizophrenia has increased higher and as of 2016, the number of prevalent cases was approximately 20.9 million globally.[2] Due to the chronic nature of schizophrenia, patients usually require life-long treatment,[3] and antipsychotic drugs are the main choice for schizophrenia. In the current guidelines for the treatment of schizophrenia, second generation antipsychotic drugs (SGAs) are recommended as the first-line treatment.[4–6]

Blonanserin is a novel SGA for the treatment of schizophrenia that received approval in Japan in 2008, Korea in 2009, and China in 2017.[7] The recommended dosage for maintenance therapy is 4–8 mg twice per day. Blonanserin exhibits high receptor selectivity, showing a strong affinity for dopamine D2 and D3 receptors, as well as 5-HT2A receptors, which has a good curative effect on both the positive and negative symptoms of schizophrenia and may improve some cognitive symptoms and social function of patients. Conversely, it demonstrates a comparatively lower affinity for serotonin 5-HT2C, adrenaline α1, muscarinic M1 and histamine H1 receptors.[8–10]

Pharmacokinetic studies have showed that blonanserin is rapidly absorbed, reaching the maximum plasma concentration (C_{max}) about 1.5 hours following oral administration. The plasma protein binding rate of blonanserin is almost 100%.

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Blonanserin is metabolized mainly by cytochrome p450 3A4 into a variety of metabolites in the liver. The majority of blonanserin is excreted through urine (59%) and feces (30%) in metabolized forms, with less than 5% excreted unchanged in the feces. After a single dose, the terminal elimination half-life ($t_{1/2}$) of blonanserin in plasma is approximately 12 hours.[10,11]

Upon examination of a pharmacokinetic study conducted on male healthy Japanese subjects,[10] it was determined that the AUC_{0-t} for blonanserin in a fasting state was 0.91, 2.82, and 6.34 μg·h/L for dosages of 4, 8, and 12 mg, respectively. The corresponding half-life values were 10.7, 12.0, and 16.2 hours. Nevertheless, a significantly elevated exposure to blonanserin was noted in Chinese subjects following a single administration of 8 mg, as compared to the data from Japanese subjects.[11]

The pharmacokinetic characteristics of drugs can be influenced by various factors, including age, gender, ethnicity, food, dosage, disease status and drug combination.[12–14] Previous researches have revealed variations in the pharmacokinetic profiles of blonanserin when consumed with food, grapefruit juice, and alcohol in Chinese population.[15,16] However, the research results on the pharmacokinetic effect of food vary greatly. In a population pharmacokinetic analysis, the bioavailability increased 1.82-fold by fed relative to fasting intake.[17] While another study found that a high-fat meal increased the bioavailability of blonanserin by 5.2 times.[18]

Given that altered bioavailability can affect both the efficacy and toxicity of a drug, it is essential to investigate the degree to which a high-fat meal affect the pharmacokinetic parameters of blonanserin in the Chinese population. Therefore, we conducted a study to assess the effect of food on the pharmacokinetics and safety of blonanserin in healthy Chinese subjects.

Materials and Methods

Ethics Statement

The bioequivalence study of blonanserin was carried out at the Phase I Clinical Research Center of Hebei General Hospital from March to June 2023. The study protocol was reviewed and approved by the Medical Ethics Committee of Hebei General Hospital. The study protocol and any modifications were authorized by the Ethics Committee of Hebei General Hospital (approval No. 2023-02, 2023-03). The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines (2023), the Guidelines for Good Clinical Practice (2020), and the Declaration of Helsinki (2013). Before the trial, all subjects were informed about the study procedures, potential risks, and benefits, and provided written informed consent.

The bioequivalence study was registered on the Chinese Clinical Trial website [http://www.chinadrugtrials.org.cn/index.html] (number: #CTR20230703, registered date: Mar 13, 2023). The Chinese Clinical Trial website is commonly used, but it is unfortunately not recognized by the WHO. So the bioequivalence clinical trial was retrospectively registered at the Chinese Clinical Trial Registry which is recognized by the WHO [https://www.chictr.org.cn/] (number: ChiCTR2400082289 and ChiCTR2400082119, registered date: Mar 26, 2024 and Mar 21, 2024).

Subjects

Healthy male and female Chinese subjects aged 18 years or older, with a body mass index (BMI) ranging from 19 to 26 kg/m^2 (≥ 50 kg for males and ≥ 45 kg for females) were enrolled in the screening period. The overall health status of the participants was evaluated by physicians, considering various factors such as routine physical examination, vital sign measurement, medical history, laboratory tests, 12-lead electrocardiography, and chest radiography. Subjects were excluded from participating in this study if they had a history of cardiovascular, endocrine, neurological, gastrointestinal, pulmonary, haematological, immunological, urogenital, psychiatric, or peripheral vascular diseases; abuse of drug, nicotine, or alcohol; a history of blood donation or acute loss of blood exceeding 400 mL within the past three months; postural hypotension. In addition, female subjects who were pregnant or lactating during the study period, or planning to be pregnant within one month before dosing until six months after the end of the study were also excluded.

Study Design

The bioequivalence study was a single-center, randomized, open-label, single-dose, two-sequence, two-period cross-over trial design, which consisted of two independent trials: a fasting trial and a postprandial trial. In both trials, eligible subjects were randomly assigned to either the T-R or R-T group with a 1:1 ratio, based on a random number table

Table 1 High-Fat Meal Details

Nutrients	Protein (g)	Fat (g)	Carbohydrates (g)
Cheesy beef burger	30	49	43
Hash browns	1	11	15
Chicken porridge	5	4	4
Total (g)	36	64	62
Calories (KCal)	144	576	248
Percentage of calories (%)	14.9	59.5	25.6
Total calories (KCal)	968		

Notes: 1 g protein was calculated by 4 kcal calories, lg fat by 9 kcal calories, and 1 g carbohydrate by 4 kcal calories. Cheesy beef burger, Hash browns and Chicken porridge all come from McDonald.

generated by SAS statistical software (v 9.4). Here, T represented the test drug from Hebei Longhai Pharmaceutical Co., LTD and R was the reference drug produced by Sumitomo Dainippon Pharma Co., Ltd. Suzuka Plant. There was a 14-day washout period between 2 drug administration phases. In the fasting trial, subjects were given a single dose of the test or reference tablet, administered orally with 240 mL warm water after a overnight fast for at least 10 hours, while in the postprandial trial, they consumed a high-fat and high-calorie standard meals (totaling about 800–1000 kcal, comprising 150 kcal from protein, 250 kcal from carbohydrates, and 500–600 kcal from fat, the meal composition was detailed in Table 1) 30 minutes prior to drug administration and followed the same scheme. Water intake was restricted to 1 hour before and after drug intake. Subjects were required to maintain an upright position for 4 hours post-administration. Standardized meals were provided 4 and 10 hours after drug administration.

Previous researches indicated that the inter-individual coefficient of variation for blonanserin is approximately 30%. It was posited that the geometric mean ratio of the test (T) to reference (R) would fall between 0.95 and 1.05, with a coefficient of variation (CV) of 30%. The requisite sample size to ascertain bioequivalence boundaries of 80.00% to 125.00% between T and R, with 80% power at a significance level of 5%, was ascertained. Factoring in an attrition rate of approximately 20% and the impact of food on pharmacokinetics, it was determined that a sample size of 56 subjects in the fed group and 50 in the fasted group would be adequate to satisfy statistical demands.

To eliminate deviation of products from different manufacturers, the pharmacokinetic parameters of all subjects who took R preparation for the first time in the fasting and postprandial trials were selected and analyzed to evaluate the impact of food on the bioavailability of blonanserin. Figure 1 shows the screening and inclusion distributions of the participants in the fasting and postprandial trials.

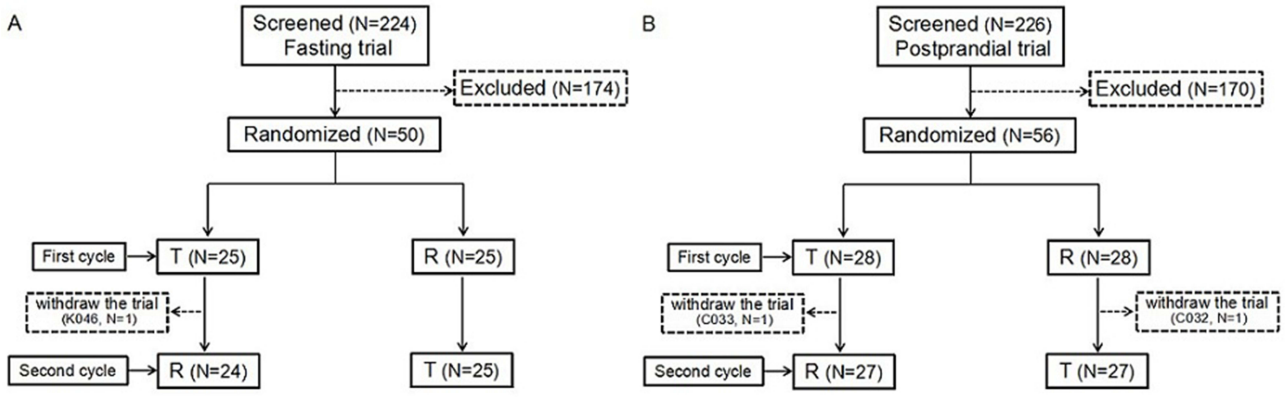

Figure 1 Subjects flow chart. Flow chart of the subjects in the fasting trial (**A**). Flow chart of the subjects in the postprandial trial (**B**).
Abbreviation: N, the number of subjects.

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Blood Sample

In the fasting trial, blood samples of 4 mL each were collected in K_2-EDTA anticoagulant tubes at various time points, including pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, and 72 hours post-dose. Similarly, during the postprandial trial, blood samples of 4 mL each were collected in K_2-EDTA anticoagulant tubes at pre-dose and at 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 24, 48, and 72 hours post-dose. Within 60 minutes of collection, blood samples were centrifuged at 1700g for 10 minutes at 4°C to separate the plasma, which was then stored at −80°C until use.

Bioanalytical Methods

A validated LC-MS/MS method, followed by liquid-liquid extraction, was employed to measure the plasma concentrations of blonanserin in healthy subjects. LC-20ADXR (Shimadzu, Japan) and a TRIPLE QUAD 6500+Low Mass Spectrometer with ESI source (AB SCIEX, USA) were used. Blonanserin-d5 served as the internal standard for the assay.

The analytes were separated using an ULTIMATE XB C18 column (5.0μm, 2.1×50mm) with gradient elution at a flow rate of 0.8 mL/min. The mobile phases consisted of A (0.1% acetic acid in water) and B (0.1% acetic acid in acetonitrile). The column temperature was maintained at 40 °C. The m/z was 368.3/297.2 for blonanserin and 373.3/297.2 for blonanserin-d5. The optimal instrument settings were as follows: Heater temperature at 550 °C; ion spray voltage as 5500 V; declustering potential as 100 V for blonanserin and 70 V for blonanserin-d5 (IS); collision energy as 38 V for blonanserin and 40 V for blonanserin-d5 (IS). Curtain gas as 40 psi, and gas 1 and gas 2 were both set as 55 psi.

The linear range for blonanserin was 2.00 pg/mL to 2000 pg/mL. The lower limits of quantitation (LLOQ) of blonanserin was 2.00 pg/mL. The intra-batch and inter-batch precision of blonanserin in plasma samples were less than 7.2% and 5.3%, respectively. The intra-batch and inter-batch accuracy of blonanserin were in the range of −4.1% to 9.5% and −2.0% to 4.4%.

Safety Evaluations

Safety assessments encompassed critical indicators such as vital signs (blood pressure, pulse, and temperature), physical examination, 12-lead electrocardiogram (ECG), laboratory examination, adverse events (AEs), and concurrent medication. Any adverse events (AEs) experienced by the subjects were meticulously tracked by the research doctors and voluntarily reported by the subjects themselves. The severity of AEs was categorized according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 5.0), version 5.0. The causality of AEs was evaluated as five categories: unrelated, unlikely, possibly, probably, or definitely related.

Statistical Analysis

The non-compartmental method (NCA module) of Phoenix WinNonlin Version 8.0 software (Pharsight Corporation, Sunnyvale, CA, USA) was used to calculate the pharmacokinetic parameters of blonanserin, including C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, T_{max}, V/F and CL/F. The Linear Up-Log-Down trapezoidal method was used for AUC calculation. The BE module of WinNonLin was used to analyze AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of blonanserin under fasting and fed conditions after logarithmic conversion. According to the technical guidelines for food-effect studies during new drug development issued by China's NMPA,[19] the least-square geometric mean (LSGM) ratio of the primary PK parameters (fed/fasting) and the 90% confidence interval (CI) were used to evaluate the effect of a high-fat meal on the pharmacokinetics of blonanserin (The LSGM value was obtained by calculating the exponential function of the mean logarithmic difference of PK parameters under the fed condition and the fasting condition). To align with both NMPA guidance and traditional *t*-tests, we presented results from both methods, demonstrating concordance in significance. The means of the pharmacokinetic parameters were compared using independent samples *t*-test. To control for Type I error inflation, a Bonferroni correction was applied to account for multiple testing. A Pearson's chi-square test was performed to compare the incidence rates of drug-related AEs between the fasting and fed conditions, with statistical significance determined at $P < 0.05$.

Table 2 Demographic and Baseline Information of Subjects

Variables	Statistics	Fasting Trial	Postprandial Trial
Age (years)	Mean (SD)	30.04(8.39)	34.25(9.56)
Sex n (%)			
Male		40(81.63)	40(72.73)
Female		9(18.37)	15(27.27)
Height (cm)	Mean (SD)	168.94(6.43)	166.76(7.53)
Weight (kg)	Mean (SD)	64.85(8.23)	64.20(8.63)
BMI (kg/m^2)	Mean (SD)	22.66(1.97)	22.99(1.84)

Results

Subjects

A total of 224 subjects entered the fasting screening period, while 226 subjects entered the postprandial screening period. Finally, 50 subjects were assigned to the fasting trial (male: 41, female: 9), and 56 subjects were selected for the postprandial trial (male: 41, female:15). One subject in the fasting trial and another one subject in the postprandial trial withdrew before eating R preparation. Owing to the absence of data resulting from participant attrition or exclusion for a variety of reasons, this study did not employ any method for data imputation. As a result, data of 49 and 55 subjects in fasting and postprandial trials respectively were used to evaluate the effect of food on the pharmacokinetics of blonanserin. The demographic and baseline characteristics of subjects in fasting and postprandial trials are presented in Table 2.

Pharmacokinetic Evaluations

The plasma concentration-time profiles of blonanserin in healthy Chinese subjects after a single oral dose of blonanserin tablet under fasting and fed conditions are shown in Figure 2. The box plots of the main pharmacokinetic parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$) under fasting and fed conditions are shown in Figure 3.

The pharmacokinetic parameters of blonanserin, including the primary endpoints (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$) and the secondary endpoints (T_{max}, $t_{1/2}$, V/F, CL/F, and MRT) are shown in Table 3. Mean (± standard deviation) C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ of blonanserin in plasma after a high-fat meal were 1031.56 ± 490.81 pg/mL, 7247.83 ± 2755.25 pg×h/mL, and

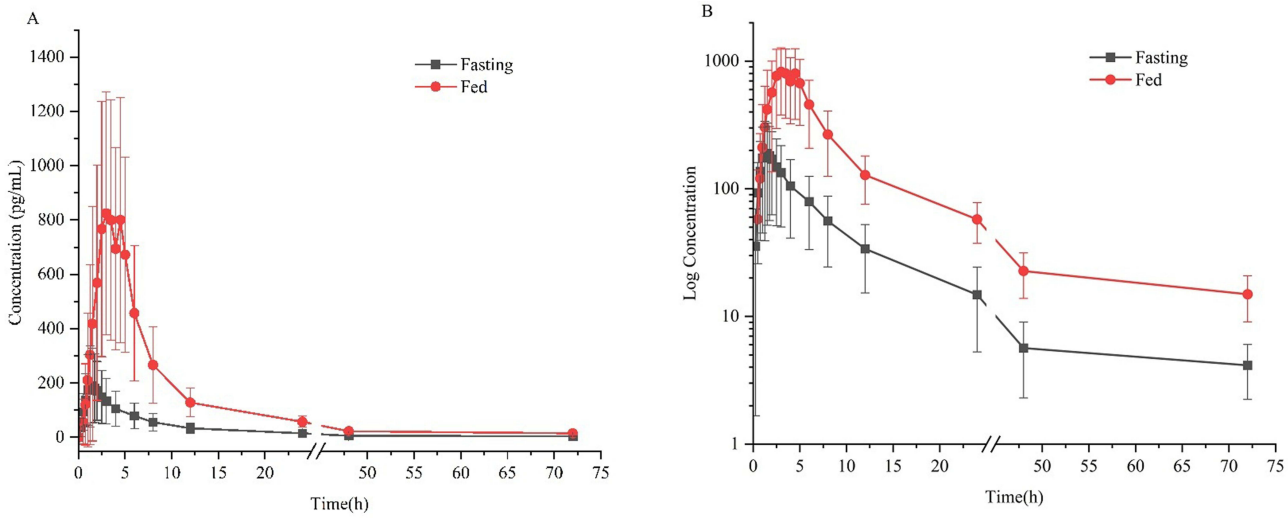

Figure 2 Mean plasma concentration (±SD) versus time profiles of blonanserin after single oral dose administration of blonanserin tablet (4 mg) under fasting and fed conditions: Arithmetic mean (**A**) and log transformation (**B**).

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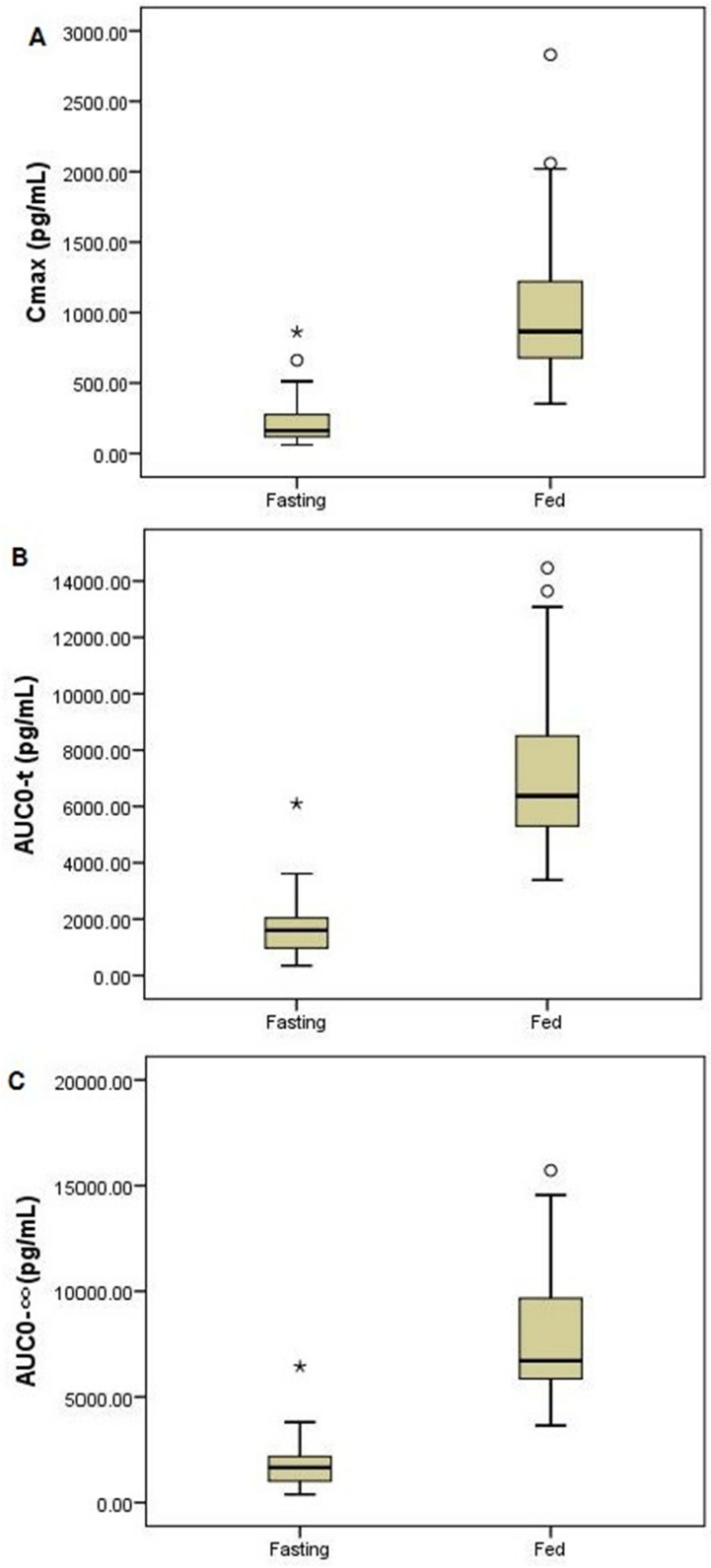

Figure 3 Box plots of the main pharmacokinetic parameters: C_{max} under fasting and fed conditions (**A**). AUC_{0-t} under fasting and fed conditions (**B**). $AUC_{0-\infty}$ under fasting and fed conditions (**C**).

Table 3 Pharmacokinetic Parameter Values for Blonanserin

PK Parameters	Arithmetic Mean (SD)		Geometric Mean (CV (%))		LSGM Ratio Fed/ Fasting (90% CI)[c]	p-value (Raw)	Significance (α=0.00625)
	Fasting[a]	Fed[b]	Fasting[a]	Fed[b]			
C_{max} (pg/mL)	216.33 (151.94)	1031.56 (490.81)	179.08 (70.24)	936.16 (47.58)	5.23 (440.59–620.29)	0.000*	Yes
AUC_{0-t} (pg×h/mL)	1663.87 (995.26)	7247.83 (2755.25)	1422.01 (59.82)	6788.80 (38.01)	4.77 (408.80–557.53)	0.000*	Yes
$AUC_{0-\infty}$ (pg×h/mL)	1759.97 (1045.81)	7763.66 (2959.70)	1508.98 (59.42)	7267.53 (38.12)	4.82 (412.94–561.73)	0.000*	Yes
$t_{1/2}$(h)	16.58 (5.62)	21.84 (5.99)	15.68 (33.89)	20.74 (27.40)	1.32 (117.60–148.72)	0.000*	Yes
T_{max} (h)[d]	1.25 (0.5,3)	3 (1,5)	–	–	–	0.000*	Yes
V/F (L)	65,604 (26,303)	18,438 (7664)	59,967 (40.09)	16,466 (41.57)	–	0.000*	Yes
CL/F (L/h)	3126 (1996)	586 (203)	2651 (63.83)	550 (34.71)	–	0.000*	Yes
MRT(h)	16.74 (3.58)	19.16 (4.04)	16.32 (21.39)	18.66 (21.07)	–	0.002*	Yes

Notes: [a]Fasting = blonanserin tablet (4 mg) administered in fasting state. [b]Fed = blonanserin tablet (4 mg) administered after high-fat meal. [c]Mean, ratio, and CI are based on geometric means because data are analyzed on log scale. [d]Values are medians (minimum–maximum). *p < 0.00625 (Bonferroni-adjusted).

Abbreviations: AUC_{0-t}, area under the concentration–time curve from zero to the final measurable concentration; $AUC_{0-\infty}$, area under the concentration–time curve from time zero to infinity; Cmax, maximum concentration; $t_{1/2}$, elimination half-life; Tmax, Time to reach maximum concentration; V/F, Volume; CL/F, renal clearance; MRT, mean residence time; SD, standard deviation; CV, coefficient of variation; CI, confidence interval.

7763.66 ± 2959.70 pg×h/mL respectively. These values were higher compared to those obtained under fasting conditions, which were 216.33 ± 151.94 pg/mL, 1663.87 ± 995.26 pg×h/mL, and 1759.97 ± 1045.81 pg×h/mL, respectively. Furthermore, the V/F and CL/F values of blonanserin in plasma decreased after a high-fat meal to 18,438 ± 7664 L and 586 ± 203 L/h, respectively, compared to 65,604 ± 26,303 L and 3126 ± 1996 L/h under fasting conditions. In addition, co-administration of blonanserin with food resulted in an extended $t_{1/2}$ from 16.58 to 21.84 h.

Effect of a High-Fat Meal on the Pharmacokinetics

The LSGM ratio of blonanserin, along with their 90% confidence interval (CI) between fasting and fed conditions are shown in Table 3.

The C_{max} of blonanserin in plasma after a high-fat meal increased by 5.23 times relative to the fasting conditions. Similarly, the AUC_{0-t} and $AUC_{0-\infty}$ of blonanserin after a high-fat meal rose by 4.77-fold and 4.82-fold, respectively. The 90% CIs of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ between fasting and fed conditions ranged from 440.59–620.29, 408.80 to 557.53 and 412.94 to 561.73, which were outside the 80.00–125.00% range. To enhance the robustness of the research outcomes, the 95% CIs for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were computed for both fasting and fed states, yielding the following ranges: 426.14 to 641.32, 396.63 to 574.64, and 400.74 to 578.83, respectively. Additionally, in comparison to fasting conditions, the T_{max} was delayed by 1.75 hours after consumption of a high-fat meal. The mean $t_{1/2}$ was extended by 5 hours when blonanserin was administered with a high-fat meal as opposed to administration without food. Furthermore, the V/F and CL/F in the postprandial state were lower than that in the fasting state. All measured pharmacokinetic parameters showed statistically significant differences between fasted and fed conditions ($p < 0.05$). After applying Bonferroni correction, the significance threshold was set at $p < 0.00625$ ($\alpha = 0.05/8$). Notably, all evaluated pharmacokinetic parameters maintained statistical significance ($p<0.00625$) following stringent Bonferroni adjustment (Table 3). These findings indicated that a high-fat meal had a significant effect on the pharmacokinetics of blonanserin.

Safety Evaluations

During the postprandial trial, one serious AE (fracture of foot) occurred, which led to the discontinuation of the study drug. However, it was unrelated to the study drug. Administration of a single oral dose of blonanserin tablet of 4 mg was found to be safe and well tolerated in healthy subjects. The AEs observed in the fasting and postprandial trials are summarized in Table 4.

Table 4 Summary of AEs in Healthy Subjects in Fasting and Postprandial Trials

Parameters	Fasting Trial (n=50)			Postprandial Trial (n=56)		
	AE count	%	n	AE count	%	n
Sum	28	32.0	16	58	67.9	38
AE severity						
Grade 1	24	26.0	13	57	66.1	37
Grade 2	3	4.0	2	0	0	0
Grade 3	1	2.0	1	1	1.8	1
Correlation with drugs						
Possible related	17	24.0	12	25	28.6	16
Possible unrelated	11	8.0	4	323	37.5	21
Definitely unrelated	0	0	0	1	1.8	1
Influenza	1	2.0	1	0	0	0
Upper respiratory infection	0	0	0	1	1.8	1
White blood cell count decreased	1	2.0	1	0	0	0
ALT elevated	1	2.0	1	3	5.4	3
AST elevated	3	6.0	3	3	5.4	3
Lymphocyte % decreased	1	2.0	1	1	1.8	1
Blood bilirubin elevated	0	0	0	2	3.6	2
Conjugated bilirubin elevated	0	0	0	2	3.6	2
Blood cholesterol elevated	0	0	0	2	3.6	2
HGB decreased	0	0	0	1	1.8	1
MCHC decreased	0	0	0	1	1.8	1
Urine leukocyte positive	2	4.0	1	0	0	0
Urinary sediment detected	1	2.0	1	0	0	0
Urine erythrocyte positive	2	4.0	2	0	0	0
Urine occult blood positive	2	4.0	2	0	0	0
Eosinophils % elevated	2	4.0	2	1	1.8	1
Eosinophil count increased	1	2.0	1	1	1.8	1
ECG abnormality	2	4.0	2	5	9.0	5
TG increased	5	10.0	5	5	8.9	5
Serum potassium elevated	1	2.0	1	0	0	0
Blood pressure increased	1	2.0	1	0	0	0
Neutrophil count decreased	2	4.0	2	0	0	0
Creatinine increased	0	0	0	2	3.6	2

(*Continued*)

Table 4 (Continued).

Parameters	Fasting Trial (n=50)			Postprandial Trial (n=56)		
	AE count	%	n	AE count	%	n
Serum phosphorus decreased	0	0	0	8	14.3	8
GLU decreased	0	0	0	12	21.4	12
GLU increased	0	0	0	1	1.8	1
FIB decreased	0	0	0	1	1.8	1
FIB increased	0	0	0	1	1.8	1
Platelet count increased	0	0	0	1	1.8	1
BUA increased	0	0	0	2	3.6	2
Anemia	0	0	0	1	1.8	1
Fracture of foot	0	0	0	1	1.8	1

In the fasting trial, there were 16 cases of AEs (32.0%) and 12 (24.0%) were related to the study drug. In the postprandial trial, there were 38 cases of AEs (67.9%), with 16 (28.6%) linked to the study drug. The drug-related AEs included elevation of blood pressure, mild laboratory abnormalities such as increases in alanine aminotransferase, aspartate aminotransferase, bilirubin, cholesterol, blood glucose, serum potassium, triglyceride and platelet count, as well as decreases in hemoglobin, white blood cell count, and neutrophil count. ECG abnormalities, including sinus bradycardia and supraventricular extrasystole were also noted. Among these, aminotransferase elevation was the most common AE, and the majority of AEs were of mild intensity and transient in nature. Specifically, during the fasting trial, two AEs involving decreased neutrophil counts were categorized as grade 2 and grade 3, respectively. While one AE concerning a reduced white blood cell count was classified as grade 2. All three of these AEs were related to the study drug. Overall, the incidence of drug-related AEs was similar between the postprandial trial and the fasting trial (P=0.594).

Discussion

Food intake are commonly considered to be factors that can influence the pharmacokinetic characteristics of drugs, resulting in variations in systemic exposure. However, the impact of food on the pharmacokinetic profiles of blonanserin specifically in the Chinese population exhibited considerable variability across various studies.

Blonanserin is formulated for oral administration in individuals with schizophrenia. Similar to other orally administered drug, assessing the impact of food on its bioavailability is important for offering dosing recommendations. The study focused on investigating how a high-fat meal influences the oral bioavailability of blonanserin tablets. Typically, the effect of food on drug bioavailability is evaluated under meal conditions anticipated to exert the greatest effects on the pharmacokinetics of drugs, therefore, a high-fat and high-calorie meal is recommended by regulatory agencies.

In the study, we investigated the effect of food on blonanserin pharmacokinetics in healthy Chinese subjects. In order to reduce the formulation interference from different manufacturers, pharmacokinetic data of the reference product were evaluated. The results proved that the C_{max} and AUC of blonanserin after a high-fat diet had about 5-fold over that in the fasting state, the 90% CIs of C_{max} and AUC were all outside 80.00–125.00%. Besides, relative to the fasting conditions, the T_{max} and $t_{1/2}$ were also significantly extended after a high-fat high-calorie diet. These observations suggested that food dramatically increased blonanserin exposure, and also significantly prolonged the lag time of absorption and elimination. The results of our study provide key operational guidance for designing follow-up multiple-dose trials, including dose regimen determination, sampling time optimization, and dietary standardization.

The significant food-related increases in exposure of blonanserin observed in the present study were higher than those reported by Saruwatari et al.[20] They investigated the effect of food on the pharmacokinetics of 2 mg blonanserin in

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Japanese and found that Cmax and AUC increased by 330% and 386%, respectively, in the postprandial state. However, no significant differences in Tmax and $t_{1/2}$ were observed between fasting and postprandial states at this dosage. Chen et al[21] indirectly compared the pharmacokinetic parameters of a single 2mg dose after a meal and a single 4 mg dose in a fasting state in the Chinese population, and discovered a comparable Cmax and AUC of the two cases. Nevertheless, the specific extent of the influence of food on the pharmacokinetics of blonanserin was undetermined. Furthermore, the study in Chinese examining the pharmacokinetic impact of food on an 8 mg dose of blonanserin reported more modest increases in AUC and Cmax.[15] Specifically, high-fat meals led to a 2.58-fold increase in AUC and a 2.4-fold increase in Cmax for blonanserin, when compared to the reference period. Meanwhile, a significant prolongation of $t_{1/2}$ was observed in this study (from 9.7 to 17.6h) after a high-fat meal, which was longer than that in our study. Similarly, findings from the population pharmacokinetic study indicated that dietary intake could enhance the bioavailability of 8 mg blonanserin by 1.82 times.[17]

Regarding the 4-mg dose of blonanserin, the results in our study are similar to the research by Lei et al, which examined the influence of food consumption on the bioavailability of 4 mg blonanserin in Chinese healthy subjects. They found that subsequent to the ingestion of a high-fat diet, the bioavailability of blonanserin underwent a significant elevation, reaching a level 5.2 times greater than baseline.[18] Upon conducting an analysis, it was determined that the case numbers in the two studies were nearly identical, and the blonanserin dosage was consistent. However, the study by Lei et al focused principally on establishing bioequivalence between the test and reference formulations, omitting a detailed exposition of the food impact study.

The observed variability in high-fat diet effects on blonanserin pharmacokinetics across studies may be attributed to the composition of the high-fat diet, the dosage of the medication, or the discrepancies in sample sizes among the research cohorts. Notably, our analysis of available clinical data reveals that the food-induced bioavailability enhancement is most pronounced at the 4-mg dose level, demonstrating significantly greater exposure increases compared to both lower (2mg) and higher (8mg) dosage forms. This non-linear dose-response relationship suggests potential saturation of absorption mechanisms at higher doses, though the exact physiological basis requires further mechanistic investigation.

Food has multiple impacts on the absorption of many orally administrated drugs.[22] Dietary intake could cause physiological changes, such as changes in production, stomach acidity, and gastrointestinal motility, which could affect drug absorption and bioavailability. The physiological parameters of the gastrointestinal tract after a high-fat meal were significantly different from those during fasting.[23] Eating could increase gastric juice pH level and delay gastric emptying, reducing the dissociation of the alkaline drug blonanserin in the stomach and increasing the retention time of the stomach, thereby enhancing the absorption of blonanserin. The double-peak of blood concentration observed in the postprandial conditions may be related to delayed gastric emptying. In addition, food intake may indirectly decrease the presystemic clearance of blonanserin by increasing regional blood flow or transport of drugs through the lymphatics, thus increasing the bioavailability of drug.[24] When comparing the pharmacokinetic effects of food on various doses of blonanserin, a smaller proportion of increase in AUC and a longer half-life were observed with higher doses, suggesting some receptor-mediated uptake mechanism except for passive infusion might occur when blonanserin entering intestinal endothelial cells.

Apart from dietary effects, blonanserin, being a substrate of CYP3A4, is subject to alterations in its in vivo exposure due to the presence of inducers and inhibitors of CYP3A4.[10] Consequently, any factors that modulate CYP3A4 activity could potentially influence the pharmacokinetics of blonanserin. Furthermore, research has substantiated that alcohol can enhance the bioavailability of blonanserin by 2.4-fold.[16] Therefore, it is imperative to pay attention to the impact of concurrent medication and alcohol consumption on the bioavailability of blonanserin. Given that schizophrenia necessitates prolonged treatment, and considering the implications of variable bioavailability on both efficacy and toxicity,[25,26] the findings of this study underscore the necessity for dose adjustment of blonanserin in accordance with dietary intake.

The incidence of AEs was more higher in the high-fat meal group, while ADR was similar between the fasted group and the high-fat meal group. These results indicated that food dose not affect the safety of blonanserin. Aminotransferase elevation was the most common ADR. Therefore, attention should be given to the level of liver function in patients

taking blonanserin. However, due to the small sample size, it is necessary to conduct further studies with a larger cohort to verify the impact of food on the safety of blonanserin.

Our study has several limitations worth noting. Firstly, the study focused on assessing the effects of food on the PK characteristics of blonanserin tablets following a single dose. Secondly, the study did not explore the effects of food on the PK characteristics of blonanserin tablets in schizophrenia patients, which might be different from healthy subjects. Thirdly, while we have comprehensively characterized the food effect on blonanserin pharmacokinetics, it should be noted that the potential influence of other covariates remains to be systematically investigated in future studies. Therefore, further studies investigating the effects of food and other confounding factors on its PK characteristics after repeated administration in schizophrenia patients are needed. We are now actively planning another study to address these important questions.

Conclusion

In conclusion, administration of blonanserin at a single dose of 4 mg with meals decreased the rate of absorption and significantly increased the Cmax and AUC of blonanserin by approximately 5-fold. The single-dose oral administration of blonanserin was deemed safe and well tolerated by the majority of healthy subjects, regardless of whether they were in a fasted or fed state. The marked impact of food on the bioavailability of blonanserin should be considered when establishing dosing regimens for clinical treatment.

Data Sharing Statement

The data set used during the current study is available from the corresponding author (Huizhen Wu and Wanjun Bai) upon reasonable request.

Informed consent was written by all individual participants included in the study.

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Disclosure

The authors have declared that no competing interests exist.

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