Effect of timing of dosing in relation to food intake on systemic exposure to blonanserin, a novel potent dopamine D_2 and serotonin 5-HT_2 antagonist, in healthy volunteers

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A concise and informative title: Time effects of food intake on blonanserin absorption

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Abstract

Purpose Blonanserin is a novel potent dopamine D_2 and serotonin 5-HT_2 antagonist for the treatment of schizophrenia. The aim of this study was to investigate the prandial effects on the systemic exposure to blonanserin in healthy volunteers with particular attention to the effect of the timing of dosing relative to meal intake.

Methods Volunteers received a single 2-mg oral dose of blonanserin under the following conditions: fasting, 30 min before eating a standard meal, or 30 min, 2 h or 4 h after eating the meal. Plasma concentrations of blonanserin were measured using validated high-performance liquid chromatography coupled to tandem mass spectrometry.

Results The ratios and 90% confidence intervals of the geometric means compared to the fasting condition indicated that the maximum concentrations of blonanserin (C_{max}) significantly increased with dosing 30 min before meal intake, 30 min, 2 h and 4 h after meal intake, yielding by 330, 239, 272 and 138%, respectively. The truncated area under the concentration-time curve (AUC_{last}) also increased by 386, 201, 256 and 155%, respectively. There was no difference in the values of the time to reach maximum concentration between the fasting and the four fed states.

Conclusions Food intake increased the systemic exposure to blonanserin by more than twofold for all time intervals investigated in this study. Our results suggest that blonanserin can be administered between 30 min before and 4 h after eating, or immediately before bedtime as a 4-h interval between

the evening meal and bedtime is normal.

Keywords: food, time, dopamine D_2 and serotonin 5-HT$_2$ antagonist, blonanserin, systemic exposure

Introduction

Blonanserin [2-(4-ethyl-1-piperazinyl)-4-(4-fluorophenyl)-5,6,7,8,9,10-hexahydrocycloocta [*b*]pyridine, AD-5423] is a novel atypical antipsychotic agent, structurally unrelated to existing atypical drugs such as risperidone and clozapine [1-2]. Blonanserin has been shown to have potent dopamine D_2 and serotonin 5-HT_2 antagonist properties, while it is almost devoid of histamine H_1 and muscarinic M_1 antagonist activities [1]. Clinical trials carried out in Japan have demonstrated that blonanserin is effective in the treatment of both positive and negative symptoms of schizophrenia [2]. A recent double-blind study in a non-Japanese population reported that the drug was effective in the treatment of acute schizophrenia and showed greater efficacy for the negative symptoms compared to the placebo and to haloperidol [3]. Blonanserin was well tolerated [3-4], and its safety profile compared favourably with haloperidol, particularly with respect to prolactin elevation and the frequency of extrapyramidal symptoms [3].

Blonanserin was approved for the treatment of schizophrenia in Japan in January of 2008, and the standard maintenance dose is 4 to 8 mg given twice daily after a meal [2]. Previous phase I clinical study data show that blonanserin is rapidly absorbed and reaches the maximum plasma concentration at around 1.4 to 1.7 h [1]. In addition, the plasma elimination half-lives for blonanserin are 4.1 to 4.8 h in non-Japanese [1] and 10.7 to 16.2 h in Japanese healthy volunteers [2] under fasting conditions. To the best of our knowledge, however, there has been little information

regarding the time effects of food intake on the pharmacokinetics of blonanserin.

The aim of this study was thus to examine the systemic exposure to blonanserin after a single oral administration under fasting and fed conditions, with particular attention devoted to the effect of the timing of dosing relative to meal intake on and blonanserin absorption.

Methods

Subjects

Ten healthy Japanese volunteers (6 males and 4 females) were studied as per a protocol approved by the Ethics Committee of Hirosaki University School of Medicine after obtaining written informed consent. The mean ± standard deviation values of age was 24.2 ± 2.6 years, and the mean body weight was 54.1 ± 5.0 kg. Candidates with health problems, drug or alcohol abuse, or laboratory abnormalities on screening were excluded.

Study design

This study was conducted as a randomised, open-label, five-sequence, Latin-square crossover study with a washout interval of 2 weeks. Each subject was randomly assigned to five-sequence groups and received a single 2-mg oral dose of blonanserin (Lonasen®, Dainippon Sumitomo Pharma Co., Ltd, Osaka, Japan) with 200 mL of tap water at 9 am after an overnight fast (fasting state) or under fed conditions with a standard western meal. For the fed conditions, subjects took the drug 30 min before eating the meal (fed state 1), or 30 min, 2 h or 4 h after eating the meal (fed state 2, 3 or 4, respectively). Subjects ate the meal at 9:30 am, 8:30 am, 7:00 am or 5:00 am in fed state 1, 2, 3 or 4, respectively. The standard western meal was hamburger (722 kcal). Fat, carbohydrate and protein contents of the meal were 42.4 g (53.9%), 58.9 g (32.7%) and 20.7 g (14.4%), respectively,

based on information provided on the Web sites http://www.mcdonalds.co.jp/. No meal was allowed until 6 h after the administration of blonanserin or after breakfast for fed state 1. The consumption of alcohol, tea, coffee, cola or grapefruit juice was forbidden during the test days. A safety and tolerability evaluation was carried out by spontaneous reporting of adverse events and by using the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale for measuring unwanted effects of psychotropic drugs [5].

Sample collection and blonanserin measurement

Blood samples (10 mL each) for the determination of plasma levels of blonanserin were taken in heparinised tubes just before and 1, 2, 3, 4, 6, 8, 12 and 24 h after the administration of blonanserin. Plasma was separated immediately and stored at -30 ºC until analysis. Blonanserin (AD-5423) and [$^{2}H_{5}$]AD-5423 (an internal standard (IS)) were supplied by Dainippon Sumitomo Pharma Co., Ltd (Osaka, Japan). All reagents were purchased from Wako Pure Chemical Industries (Kyoto, Japan) except for 0.1 mol/L phosphate buffer (pH 6.8), which was purchased from Nakalai Tesque, Inc. (Kyoto, Japan). Plasma concentrations of blonanserin were determined by a validated liquid chromatography method with tandem mass spectrometry (LC/MS/MS) developed at JCL Bioassay Co. (Osaka, Japan). Briefly, blonanserin and IS were extracted from human plasma with an OASIS HLB solid phase extraction cartridge (60 mg/3 cc). After the eluate was evaporated to

dryness by centrifugal concentration, the extraction residue was reconstituted with 0.1 vol% formic acid solution/methanol (80: 20, v/ v). An a liquot o f t his so lution wa s th en injected in to t he LC/MS/MS s ystem (API4000 system) equipped with a YMC-Pack Pro C18 column. Grad ient elution was perfo rmed wi th 0 .1 vo l% fo rmic aci d sol ution/methanol (8 0:20, v/ v) an d 0.1 vo l% formic acid solution/methanol (20:80, v/v) as the mobile phases. The measurement was conducted in the multiple reaction monitoring mode with el ectrospray ionisation and positive ion detection. The method w as validated for t he c oncentration ra nge 1 0 t o 1 000 p g/mL. Intra- a nd inter-day relat ive standard deviations for a co ncentration of 10 p g/mL were 7.9% and 4.9%, respectively. The limit of quantification was 10 pg/mL.

Statistical analysis

The m aximum plasm a conce ntrations (C_{max}), the ti me to rea ch maximum conce ntration (T_{max}), the tr uncated area under the concentration-time curve from ti me 0 to the t ime of las t quantifiable concentration (AUC_{last}) calculated by linear trapezoidal summation and the elimination half-life ($T_{1/2}$) w ere esti mated usi ng no n-compartmental m ethods. S tatistical a nalyses were performed using SPSS software (v ersion 17.0, SPSS I nc., Chicago, IL, USA). The point estimate and 90% confidence interval (CI) [6-7] for the geom etric mean ratio of each fe d state relative to the fasting state in log-transformed C_{max} and AUC_{last} were calcu lated by analysis of variance (ANOVA)

using a mixed effects model fitting sequence, with period and treatment as fixed effects and subject (sequence) as a random effect. A lack of effect of food was concluded if the 90% CI was within the range of 0.80 to 1.25. The differences in the median of T_{max} were compared using the Kruskal-Wallis test. A *p*-value less than 0.05 was considered statistically significant.

Results

All plasma concentrations of blonanserin were below the limit of quantification before administration. Figure 1 shows the mean concentration-time profile of blonanserin under fasting and fed conditions, and the corresponding pharmacokinetic parameters are summarised in Table 1. Following the administration of blonanserin under the fasting condition, C_{max} was achieved at 2.0 h after dosing. Under the fed conditions, the median T_{max} was delayed to 2.7 h with dosing 30 min before meal intake (fed state 1). The median T_{max} accelerated to 1.5 h with dosing 30 min after meal intake (fed state 2) and was 2.0 h with dosing at both 2 and 4 h after meal intake (fed states 3 and 4; Figure 1, Table 1). There were, however, no significant differences between the fasting state and fed states (p>0.05).

The geometric mean ratio between fed state 1 and the fasting state was 4.30 (90% CI 2.01, 9.18) for C_{max} and 4.86 (2.31, 10.19) for AUC_{last}. The geometric mean ratio between fed state 2 and the fasting state was 3.39 (1.59, 7.25) for C_{max} and 3.01 (1.44, 6.32) for AUC_{last}. For the fed state 3 and the fasting state, the geometric mean ratio was 3.72 (1.74, 7.95) for C_{max} and 3.56 (1.70, 7.48) for AUC_{last}. Finally, the geometric mean ratio between fed state 4 and the fasting state was 2.38 (1.11, 5.08) for C_{max} and 2.55 (1.21, 5.35) for AUC_{last}. The C_{max} increased by 330, 239, 272 and 138% in fed states 1, 2, 3 and 4, respectively. The AUC_{last} also increased by 386, 201, 256 and 155% in fed states 1, 2, 3 and 4, respectively. These results showed remarkable differences in the extent of

maximum plasma drug concentrations and drug absorption rates between the fed and fasting conditions (Figure 1, Table 1).

Mild psychological side effects, e.g. concentration difficulty, latency and sleepiness, were observed from 2 to 6 h after blonanserin administration in 4 subjects under both the fasting and fed conditions; however, there was no change in the UKU score between fasting and fed conditions (data not shown).

Discussion

This is the first report of the time effects of food intake on the systemic exposure to blonanserin, a novel atypical antipsychotic agent. The findings of this study showed that food has a significant influence on the extent of absorption of blonanserin. The C_{max} and the AUC_{last} were significantly higher under all of the fed conditions investigated in this study compared to those of the fasting condition, with no significant difference in the T_{max} (Figure 1, Table 1). We thus provide evidence that the systemic exposure to blonanserin can be significantly increased if patients receive the drug between 30 min before and 4 h after meal intake.

The current study is consistent with the literature regarding the significant increases of the drug absorption when the drug is administered either concomitantly with or after eating a meal [8-13]. The findings of this study indicated that the increase of systemic exposures to blonanserin continues until at least 4 h after food intake. This is likely due to the amount of time that food, particularly fat, remains in the gastrointestinal tract (3 to 4 h) [8-9]. We can speculate the possible mechanisms of the food-effects observed in this study that, firstly, elevation of gastric pH due to food intake may increase the solubility of blonanserine, because the octanol/water partition coefficient of blonanserin increases with respect to the increase of pH up to pH 8.3 [2]. Secondly, increased splanchnic blood flow may influence absorption of drugs that are extensively metabolised as a result of changes in the clearance of drugs during the first pass through the hepatoportal system

[8-9, 13]. Thirdly, consumption of food enhances biliary activity in response to dietary fat, and the increased activity of bile salts induced by the meal improves stability of emulsion phase within the gut lumen, which increases the absorption of drugs [8-9].

Blonanserin is metabolised mainly by cytochrome P450 (CYP) 3A4 [2], and some foods, such as grapefruit juice, may inhibit this enzyme [14]. Several compounds in grapefruit juice increase the absorption of many drugs based on the inhibition of CYP3A4 in the lumen of the small intestine [14]. The mean values of C_{max} and AUC_{last} of blonanserin were increased by 1.77-fold and 1.83-fold, respectively, after ingestion of 200 ml of grapefruit juice [2]. In this study, all subjects were restricted from intake of grapefruit juice and other dietary components that affect CYP3A4 activity. The elevation of plasma concentrations of blonanserin in the fed conditions might thus be attributable to the enhanced absorption of blonanserin caused by food intake.

Previous studies have indicated that the bioavailability of some drugs is heavily influenced by the timing of meals [10-12] and may be different from the fasting state. In this study, there were remarkable differences in the C_{max} and the AUC_{last} between with dosing 30 min before, 30 min, 2 h and 4 h after meal intake (Figure 1, Table 1). However, our findings indicated that a single 2-mg oral dose of blonanserin up to 4 h after a meal results in more than 155% greater systemic exposure compared to administration of the drug under fasting conditions. The repeated doses of blonanserin showed potent striatal D_2 receptor activity in the positron emission tomography study at 5 to 15

mg/day (personal communication, Dainippon Sumitomo Pharma Co., Ltd). A recent study demonstrated that the high daily doses, 5 and 10 mg/day, of blonanserin were more effective against the negative symptom than the low dose (2.5 mg/day) under fed conditions in patients with acute schizophrenia [3]. Taken together, our results suggest that blonanserin may offer reasonable efficacy when given at dosing intervals of at least 4 h after meal intake compared to administration of the drug under fasting conditions.

The majority of patients with acute schizophrenia reported mild to moderate adverse events, such as insomnia and somnolence, after repeated oral doses (2.5 to 10 mg/day) of blonanserin, and the incidence has a tendency to increase by the amount of the daily dose of blonanserin [3]. For example, the incidences of insomnia were 4.9, 8.6 and 9.4% with the repeated daily doses of 2.5, 5 and 10 mg blonanserin, respectively [3]. In this study, mild psychological side effects were observed after a single 2-mg oral dose of blonanserin in 4 subjects under both the fasting and fed conditions; however, there was no difference in the UKU score between the fasting and fed conditions.

In conclusion, the present study suggests that the effect of food on blonanserin absorption is evident and continues with dosing from 30 min before to 4 h after eating a meal. The administration of blonanserin with long periods of fasting might reduce its efficacy, and patients should receive blonanserin between 30 min before and 4 h after eating. Moreover, our findings also suggest that blonanserin can be administered immediately before bedtime, as a 4-h interval between the evening

meal and bedtime is normal, thus avoiding psychological side effects, such as latency and sleepiness.

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Table 1 Plasma pharmacokinetic parameters of blonanserin after a single 2-mg oral administration under fasting conditions (fasting state), 30 min before meal intake (fed state 1), 30 min after meal intake (fed state 2), 2 h after meal intake (fed state 3) and 4 h after meal intake (fed state 4) (*n*=10 each).

						Ratio of adjusted means[b]			
Parameter[a]	Fasting state	fed state 1	fed state 2	fed state 3	fed state 4	fed state 1	fed state 2	fed state 3	fed state 4
C_{max} (pg/mL)	99.9 (77.4)	342 (34.1)	317 (66.0)	322 (54.8)	220 (64.2)	4.30 (2.01, 9.18)	3.39 (1.59, 7.25)	3.72 (1.74, 7.95)	2.38 (1.11, 5.08)
AUC_{last} (pg h/mL)	721 (83.4)	2766 (44.1)	1965 (77.3)	2073 (51.3)	1607 (70.7)	4.86 (2.31, 10.19)	3.01 (1.44, 6.32)	3.56 (1.70, 7.48)	2.55 (1.21, 5.35)
T_{max} (h)	2.0 (1.0-4.0)	2.7 (1.0-4.0)	1.5 (1.0-2.0)	2.0 (1.0-3.0)	2.0 (1.0-4.0)	-	-	-	-
$T_{1/2}$ (h)	11.12 ± 4.183	13.09 ± 3.473	13.52 ± 4.395	13.01 ± 4.353	14.25 ± 4.974	-	-	-	-

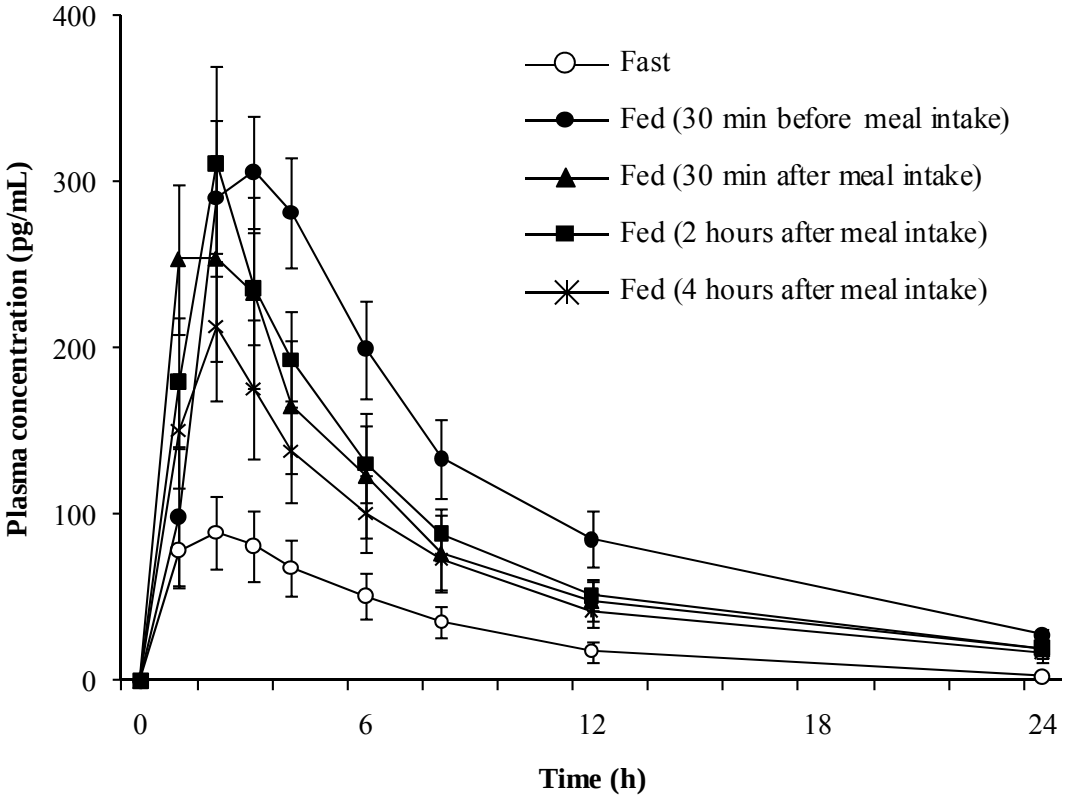
[a] C_{max}, maximumplasma concentration; AUC_{last}, area under the plasma concentration vs. time curve from time 0 to the time of the last quantifiable concentration; T_{max}, time to reach maximum concentration; $T_{1/2}$, terminal elimination half-life. C_{max} and AUC_{last} are given as geometric means with the coefficients of variation in parenthesis; T_{max} is given as the median with the range in parenthesis; $T_{1/2}$ is given as the arithmetic mean with the standard deviation ± the standard deviation.

[b] Expressed as a the geometric means compared to the fasting condition for C_{max} and AUC_{last} in the four fed states with 90% confidence interval in parenthesis.

Legends to figures

Fig. 1 Plasma concentration of blonanserin in healthy volunteers after a single 2-mg oral administration under fasting conditions (fasting state), 30 min before meal intake (fed state 1), 30 min after meal intake (fed state 2), 2 h after meal intake (fed state 3) and 4 h after meal intake (fed state 4) (mean ± standard error, *n*=10 each)

Figure 1


400
300
200
100
0
Plasma concentration (pg/mL)
0
6
12
18
24
Time (h)
Fast
Fed (30 min before meal intake)
Fed (30 min after meal intake)
Fed (2 hours after meal intake)
Fed (4 hours after meal intake)