PHARMACOTHERAPY

The Effect of Food on the Pharmacokinetics of Buspirone After Single Administration of a Sublingual Testosterone and Oral Buspirone Combination Tablet in Healthy Female Subjects

Jeroen Gerritsen, MSc,[1] Jos Bloemers, PhD,[1,2] Kim van Rooij, PhD,[1,2] Leo de Leede, PhD,[3] Ronald van der Geest, PhD,[4] Henderik W. Frijlink, PhD,[5] Hans P. F. Koppeschaar, MD, PhD,[1] Berend Olivier, PhD,[2,6] and Adriaan Tuiten, PhD[1,7]

ABSTRACT

Introduction: A new combination tablet containing sublingual testosterone and oral buspirone (T+B) was developed to benefit a subgroup of women suffering from female sexual interest/arousal disorder, caused by dysfunctionally overactive sexual inhibition.

Aim: The aim of this study was to compare the effect of food intake on the pharmacokinetics of buspirone, administered as a dual-route, dual-release combination tablet containing 0.5 mg testosterone (T) and 10 mg buspirone (B).

Methods: 19 healthy women took T+B under fed and fasted conditions during 2 overnight visits. The blood was sampled over a 24-hour period to determine the pharmacokinetics of buspirone and its active metabolite 1-(2-pyrimidinyl)piperazine (1-PP). Total testosterone levels were also assessed, at 5 time points and for quality control purposes only, as sublingual testosterone uptake is not expected to be influenced by prior food intake.

Main Outcome Measure: PK profiles of buspirone and 1-PP.

Results: For buspirone, the 90% confidence intervals (CIs) of the observed fed/fasted ratios for the plasma area under the curve $(AUC)_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} after administration of T+B were not contained within the prespecified bounds of 80% and 125%, except for the lower bound of $AUC_{0\text{-inf}}$. However, the 90% CIs of the observed fed/fasted ratios for the plasma $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} of 1-PP were contained within the prespecified bounds, with the exception of the upper bound for C_{max}. The mean AUCs and C_{max} for 1-PP did not differ between fed and fasted conditions.

Conclusions: Administration of T+B after high-caloric food intake increased the bioavailability of buspirone but did not result in differences in T_{max} when compared with fasted conditions. Both in fed and fasted conditions, T+B was generally well tolerated and safe. Exposure of 1-PP in fed and fasted conditions was comparable in both conditions. These results demonstrate that T+B can safely and effectively be used in both fed and fasted states. **Gerritsen J, Bloemers J, van Rooij K, et al. The Effect of Food on the Pharmacokinetics of Buspirone After Single Administration of a Sublingual Testosterone and Oral Buspirone Combination Tablet in Healthy Female Subjects. J Sex Med 2020;8:186–194.**

Key Words: Sublingual Testosterone; Buspirone; Food Effect; Pharmacokinetics; Female Sexual Interest; Arousal Disorder (FSIAD)

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[1]Emotional Brain B.V., Almere, the Netherlands;

[2]Utrecht Institute for Pharmaceutical Sciences and Rudolf Magnus Institute of Neuroscience, Utrecht University, Utrecht, the Netherlands;

[3]Exelion Bio-Pharmaceutical Consultancy B.V., Waddinxveen, the Netherlands;

[4]3D-PharmXchange B.V., Tilburg, the Netherlands;

[5]Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen, the Netherlands;

[6]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA;

[7]Department of Psychopharmacology, Utrecht University, Utrecht, the Netherlands

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INTRODUCTION

Low desire has consistently been reported as the most common sexual complaint in women.[1,2] It can result in sexual dissatisfaction and negatively affect psychological well-being.[3] If low desire is not caused by a mental or other medical disorder, or drug use, and if it leads to marked distress and/or interpersonal difficulties, the formal diagnosis of hypoactive sexual desire disorder may apply.[4] In the latest version of the Diagnostic and Statistical Manual of Mental Disorders-5, hypoactive sexual desire disorder was combined with female sexual arousal disorder to form female sexual interest/arousal disorder (FSIAD).[5] Despite their prevalence, few pharmacological options are available for these problems, with currently 2 drugs approved in the United States (flibanserin and bremelanotide) and none in Europe.

In an attempt to address this, 2 on-demand drug candidates were designed, based on the assumption that at least 2 different etiologies may underlie FSIAD symptoms:[6] women diagnosed with FSIAD can either have a low sensitivity for sexual cues, or they can suffer from dysfunctionally overactive sexual inhibition. A combination tablet containing sublingual testosterone and oral sildenafil (T + S) was developed specifically for the former subgroup of women,[7] whereas a combination tablet containing sublingual testosterone and oral buspirone (T+B) was developed to benefit the latter subgroup.[8] Several studies have shown these on-demand drugs to be safe and effective.[9–12] Sublingual testosterone absorption results in maximum concentration (T_{max}) within 15 minutes, followed by a return to baseline in approximately 1.5 hours.[13] This transient peak in testosterone levels has been shown to lead to increased genital and subjective responsiveness to sexual stimuli, between 3 and 6 hours later.[14,15] When sensitivity to sexual cues is increased, a central sexual response is more easily achieved which subsequently allows the phosphodiesterase-5 inhibitor sildenafil to increase genital vasocongestion. Because peripheral arousal is a strong sexual cue in itself, this would create a positive sexual responding "feedback loop" as the central processing of the peripheral cue is enhanced. The acute effects of buspirone, as well as its active metabolite, include a decrease in prefrontal serotonin levels,[16,17] which reduces inhibitory control in the prefrontal cortex, allowing for the testosterone-facilitated sexual response to occur.

Efficacy for both drugs depends on the synergistic effects of the separate components. However, the time course of the pharmacodynamics is quite different for testosterone as compared with the other components. Optimal efficacy of the combination drugs is achieved when both components act simultaneously, and because both sildenafil and buspirone become effective around 30 minutes after dose—which is in accordance with their pharmacokinetic profiles[18,19]—the separate components of the combination tablets need to be released at different times. To achieve this, the tablets are coated with testosterone for sublingual administration and have an inner core containing either sildenafil or buspirone. The core's pH-independent delayed-release matrix is designed to rupture at 2.5 hours after dose, allowing for immediate release. The pharmacokinetic profiles of the combination tablets are shown to be comparable with separate administration of the components.[7,8]

The present study focuses on T+B and is set up to investigate the effect of food intake on the pharmacokinetic profile of the combination tablet, for it is important to ensure not only exposure of the desired dose for both components but also that the therapeutic time window of 5 to 6 hours for this on-demand drug is not compromised in any way. Sublingual absorption of testosterone via the buccal mucosal membranes is not expected to be affected by food intake, as the gastrointestinal tract is bypassed. Therefore, total testosterone levels were only assessed at 5 time points and for quality control purposes only. The main focus is on the effects of food intake on the pharmacokinetics of buspirone and its main metabolite, 1-(2-pyrimidinyl)piperazine (1-PP). Like buspirone, 1-PP is a partial 5HT1a receptor agonist,[20] and it contributes substantially to the pharmacological effect of buspirone.[21–23] The effects of the intake of high-fat meals on buspirone and 1-PP were expected to be insubstantial, due to the tablet's pH-independent delayed-release matrix, which releases buspirone further on in the gastrointestinal tract. Therefore, plasma levels of buspirone and its main active metabolite were hypothesized to be similar in both fed and fasted conditions.

METHODS

Participants

A total of 20 healthy women between 18 and 55 years of age (inclusive), with a body mass index between 18 kg/m^2 and 30 kg/m^2 (inclusive), were enrolled in the study. Sufficient venous access to allow blood sampling as per protocol was required. Exclusion criteria included hypertension, use of oral contraceptives containing antiandrogens, pregnancy, abnormal liver function, and any other clinically relevant cardiovascular, respiratory, renal, hepatic, neurological, dermatological, psychiatric, or metabolic disorder.

The participants were recruited via advertisements and a volunteer database. They provided written informed consent at the screening visit, during which medical history was recorded. Furthermore, a physical examination including a 12-lead electrocardiogram was performed, urine pregnancy test and urine drug screen were performed, and standard biochemistry, serology and hematological laboratory parameters, as well as total testosterone, sex hormone—binding globulin (SHBG), albumin, thyroid-stimulating hormone (TSH), and follicle-stimulating hormone (FSH) were assessed. The first participant was enrolled on March 5, 2015, and the last participant's last visit was on 15 May 2015.

This study was carried out in agreement with the Declaration of Helsinki (264th World Medical Association General Assembly, Fortaleza, Brazil, October 2013) and the International Conference on Harmonization - Good Clinical Practice guidelines for clinical research. Approval was given by an independent

ethics committee (Stichting Beoordeling Ethiek Biomedisch Onderzoek, Assen, the Netherlands; reference number EB97) and the Dutch Competent Authority (CCMO; authorization number NL50357.056.14). The trial was registered in the European Clinical Trials Database (EudraCT number 2014-003318-99), and in the Dutch Trial Registry (Nederlands Trial Register; number NTR4862).

Study Design

The present randomized, open-label, balanced, 2-period, 2-treatment, 2-sequence crossover study in healthy female subjects was set up to evaluate the effect of food intake on the pharmacokinetics of buspirone after a single dose of T+B. In addition, safety and tolerability of T+B, administered under fed and fasted conditions, were evaluated.

The study was conducted by FlevoResearch, Almere, the Netherlands. Study staff consisted of study nurses and clinical investigators. Participants were invited to the research site for 2 overnight visits of at least 10 hours. They arrived in the evening and spent the night in a nearby hotel. They were not allowed to eat during their stay until, in the fed condition, they were served a high-fat, high-calorie meal (50% of the caloric intake of 800−1,000 kcal.) 30 minutes before drug administration. Study medication was taken with 240 ml of water. Other than that, no water intake was allowed for 1 hour before and after drug administration. Subjects were further instructed to abstain from food intake for 4 hours after drug intake. The fasted condition was similar, except that no meal was provided. In both conditions, food intake was standardized during 12 hours after dose. Administration of the drugs in both conditions was separated by a washout period of at least 1 week.

To assess the pharmacokinetics (PK) of buspirone and 1-PP, blood samples were taken before dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 14, and 24 hours after dose for each condition. Total testosterone levels were also assessed, but for quality control purposes only, at 5 time points, as sublingual testosterone uptake is not influenced by prior food intake. A final follow-up visit was scheduled after completion of the second study visit or after early discharge, within 7 to 14 days.

Medication and Dosing

T+B is a fixed-dose combination of testosterone and buspirone hydrochloride in tablet form. It is designed for sublingual and subsequent oral administration. The outer testosterone (0.50 mg) coating is released immediately and absorbed sublingually. The inner core contains buspirone (10 mg), designed for immediate release, approximately 2.5 hours after oral administration.

Subjects were given one dose of T+B in the fed condition and one in the fasted condition. The order of the conditions was randomized: based on the moment of randomization, subjects were assigned to either the "fed-fasted" or "fasted-fed" group, in alternating fashion (ie, the first subject in the fed condition during the first treatment/visit and in fasted condition during the second, the second subject fasted during the first and fed during the second, and so on). The tablets were dispensed by study staff, and drug intake was supervised to ensure treatment compliance. Subjects were instructed to keep the tablet under their tongue for 90 seconds to allow for sublingual testosterone uptake and then to swallow the tablet as a whole, without chewing or otherwise disrupting the dosage form. The amount of time that subjects had the tablet in their mouth was recorded.

BIOANALYTICAL METHODS

Plasma levels of buspirone and 1-PP, as well as testosterone and dihydrotestosterone (DHT), were determined by Analytical Biochemical Laboratory B.V. (ABL), Assen, the Netherlands. The method validation experiments were based on the Bioanalytical

Table 1. Baseline characteristics

Parameter	Value (n = 20)
Age (years)	
Mean (SD)	33.3 (10.6)
Median	34.4
Range	18.7–49.5
Age (category)	
< 40	13
40-60	7
Weight (kg)	
Mean (SD)	68.8 (7.4)
Median	69.0
Range	56.9–82.0
Menopausal status	
Postmenopausal	1
Premenopausal	19
Contraceptive use	
Hormonal	
Combined OAC	11
Implanon	1
IUS − Mirena®	0
Nonhormonal (IUD, abstinence or condoms)	7
None (post-menopausal)	1
Race	
Asian	1
Black	1
Caucasian	18
Hormones	
Total testosterone > 1.7 nmol/L − < 2.2 nmol/L	1
Total testosterone > 0.7 − 1.7 nmol/L	7
Total testosterone < 0.7 nmol/L	12
SHBG (nmol/L) (SD)	100.4 (55.2)
Albumin (g/L) (SD)	44.8 (2.6)

SHBG = sex hormone–binding globulin.

Methods Validation in Guidance for Industry: Food and Drug Administration Guidance for Industry: Bioanalytical Methods Validation, Center for Drug Evaluation and Research (May 2001).

Total Testosterone, Free Testosterone, and DHT Assays

Plasma samples for testosterone and DHT concentrations were assayed using a validated liquid chromatographic-mass spectrometric (LC-MS/MS) method with a range of 0.0500 to 20.0 ng/ml for both testosterone and DHT in human serum.

Extraction Method for Testosterone and DHT

The samples were vortex mixed, and 100 μl serum was transferred into a clean test tube to which 50 μl internal standard solution (4 ng/ml testosterone-D3 and 8 ng/ml DHT-D6) was added and vortex mixed. Subsequently, 4.5 ml 20% (v/v) dimethyl ether in n-pentane was added, tubes were capped and rotated for 20 minutes, and then centrifuged for 2 minutes at 4,700 relative centrifugal force (rcf). The tubes were placed into a cryostatic bath (−45°C), and the bottom water layer was frozen. The supernatant was transferred into a clean borosilicate tube and evaporated to dryness under a stream of nitrogen at 40°C. The residue was reconstituted in 500 μl dicholoromethane and derivatized with 2-fluoro-1-methylpyridine. The solvent was evaporated to dryness under a stream of nitrogen at 40°C. The residue was reconstituted in 30% of methanol. The obtained extract was further purified using Oasis weak cation exchange (30 mg, 1 cc) solid phase extraction cartridges. The final extract was injected for LC-MS/MS analysis.

Equipment

For the high-performance LC-MS/MS assays, an Applied Biosystem/MDS SCIEX API-4000 triple quadrupole MS, with positive multiple reaction monitoring and ion spray (turbo spray), was used. The LC system was a Shimadzu Prominence SIL-20AC HT system equipped with a Kinetix C18, 2.6μ (3.0 × 100 mm) column. Gradients of mobile phase A, B, and C were ultrapure water, 100 mM ammonium formiate buffer, and acetonitrile, respectively.

Buspirone and 1-(2-pyrimidinyl)-piperazine Assays

Plasma samples for buspirone and 1-PP concentrations were assayed using a validated high-performance LC-MS/MS method with a range of 0.0500 to 10.0 ng/mL for buspirone and 0.100−20.0 ng/mL for 1-PP in human K2EDTA plasma.

Extraction Method for Buspirone and 1-(2-pyrimidinyl)-piperazine

The samples were vortex mixed, and 100 μl plasma was transferred into a clean test tube to which 50 μl internal standard solution (5.00 ng/ml buspirone-D_8 and 40.0 ng/ml 1-(2-pyrimidinyl)-piperazine-D_8) was added and vortex mixed. Subsequently, 4.0 ml methyl *tert*-butyl ether was added, tubes were capped and rotated for 10 minutes, and then centrifuged for 2 minutes at 4,000 rcf. The tubes were placed into a cryostatic bath (−45°C), and the bottom water layer was frozen. The supernatant was transferred into a clean tube and evaporated to dryness under a stream of nitrogen at 30°C. The residue was reconstituted with injection solvent and injected for LC-MS/MS analysis.

Equipment

For the LC-MS/MS assays, an Applied Biosystem/MDS SCIEX API-4000 triple quadrupole MS, with positive multiple reaction monitoring and ion spray (turbo spray) was used. The LC system was a Shimadzu Prominence SIL-20AC HT system equipped with a Synergy Fusion-RP 75 × 4.6 mm 4.0μ high-performance liquid chromatography column. Gradients of mobile phase A, B, and C were ultrapure water, 100 mM ammonium acetate in 5% acetonitrile, and acetonitrile, respectively.

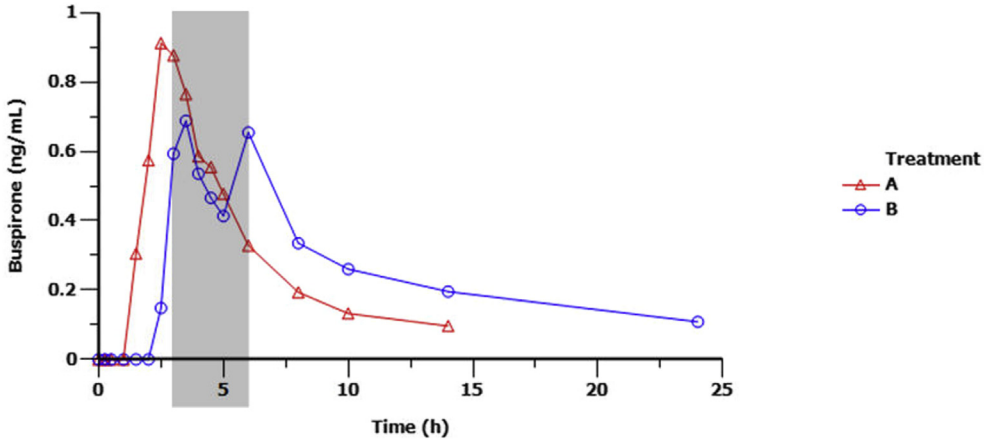

Figure 1. Arithmetic mean plasma concentration-time profile of buspirone after administration of T+B under fed and fasted conditions in healthy female subjects (linear scale). For reference only, the therapeutic window is indicated by the gray box. B= buspirone; T = testosterone. Treatment A = fed, treatment B = fasted.

Table 2. Summary of pharmacokinetic parameters of buspirone after administration of T+B in healthy female subjects in fed and fasted conditions (primary analysis)

	Fed		Fasted		Fed/Fasted	
Parameter	N	LSGM	N	LSGM	Ratio	90% CI
$AUC_{0\text{-last}}$ (hr.ng/ml)	20	3.03	19	2.32	130.31	102.32–165.97
$AUC_{0\text{-inf}}$ (hr.ng/ml)	20	3.51	17	3.19	110.07	79.60–152.21
C_{max} (ng/ml)	20	1.20	19	0.73	164.69	126.39–214.58
*T_{max} (hr)	20	3.0 (1.5–5.0)	19	3.5 (2.5–.8.0)		

AUC = area under the curve; LSMG = least-squares geometric mean. No $AUC_{0\text{-inf}}$ could be calculated for 2 subjects (fasted).
*Median, minimum, and maximum reported for T_{max}.

Hormonal Assays Performed at Screening

Standard biochemistry, serology, and hematological laboratory parameters were assessed by KCL Flevoziekenhuis, Almere, the Netherlands.

Testosterone at screening was assessed via an Elecsys electrochemiluminescence immunoassay (ECLIA) using a competition principle, with a Modular Analytics E170 module (Roche Diagnostics GmbH, Mannheim, Germany). The lower limit of detection was 0.087 nmol/l. The reference range was <2.9 nmol/l.

SHBG was assessed via an Elecsys ECLIA using a sandwich method using 2 monoclonal antibodies, with a Modular Analytics E170 module (Roche Diagnostics GmbH, Mannheim, Germany). The lower limit of detection was 0.350 nmol/l. Reference ranges for SHBG were 26.0–110 nmol/l.

FSH was assessed via an Elecsys ECLIA using a sandwich method using 2 monoclonal antibodies, with a Modular Analytics E170 module (Roche Diagnostics GmbH, Mannheim, Germany). The lower limit of detection was <0.100 mIU/ml. Reference ranges for FSH were 1.5 − 116 IU/l.

TSH was assessed via an Elecsys ECLIA using a sandwich method using 2 monoclonal antibodies, with a Modular Analytics E170 module (Roche Diagnostics GmbH, Mannheim, Germany). The lower limit of detection was 0.005 μIU/ml. Reference ranges for TSH were 0.3–4.5 mIU/l.

Albumin was assessed via a Cobas colorimetric assay using bromcresol green, with a Cobas c501 (Roche Diagnostics GmbH, Mannheim, Germany). The lower limit of detection was 2 g/l. Reference ranges for albumin were 35–52 g/l.

Statistical Analysis

For the PK of buspirone, an analysis of variance of the log-transformed area under the curve $(AUC)_{0\text{-inf}}$ and C_{max} was performed to obtain 90% confidence intervals (CIs) for the fed/fasted ratios after administration of T+B. All other data and parameters were evaluated for descriptive use only.

The primary end points in this study were $AUC_{0\text{-inf}}$ and C_{max} for buspirone. These parameters (after a single dose of T+B in fed and fasted conditions) were compared using a linear mixed effects model appropriate for a 2-period, crossover design. Period and treatment were defined as fixed effects, and subject, as a random effect. The 90% CIs, based on a t-distribution, were generated for least square geometric mean ratios (GMRs, fasted/fed) of the primary end points. Even though establishing bioequivalence was not the main goal of the study, the GMRs were compared with prespecified bioequivalence bounds of 80% and 125%, and if the

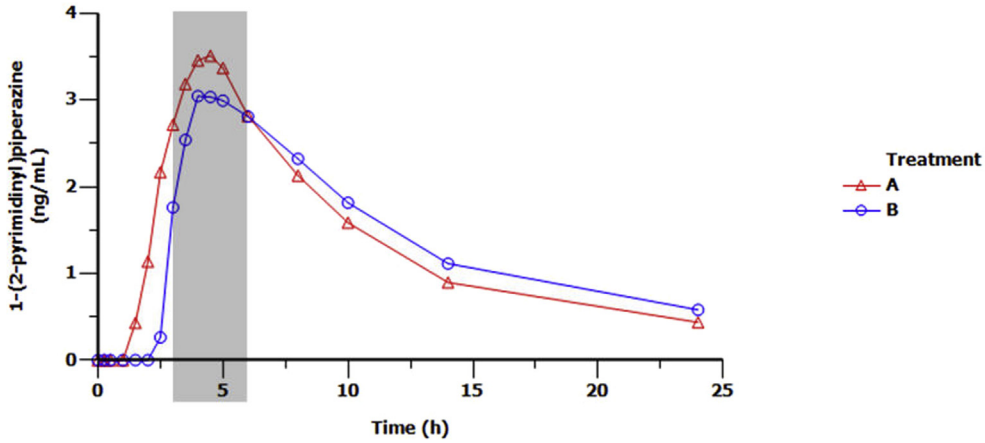

Figure 2. Arithmetic mean plasma concentration-time profile of 1-(2-pyrimidinyl)piperazine after administration of T+B under fed and fasted conditions in healthy female subjects (linear scale). For reference, the therapeutic window is indicated by the gray box. B= buspirone; T = testosterone. Treatment A = fed, treatment B = fasted.

Table 3. Summary of pharmacokinetic parameters of buspirone after administration of T+B in healthy female subjects in fed and fasted conditions (descriptive statistics)

Treatment	T_{last} (hour)	T_{max} (hour)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	$AUC_{0\text{-}inf}$* (h*ng/mL)	λ_z* (1/hour)	$t_{1/2}$* (hour)
Fed							
N	20	20	20	20	20	20	20
Mean	12.0	3.1	1.63	3.90	4.40	0.229	3.74
SD	2.80	1.13	1.25	2.66	2.84	0.141	1.54
Min	5.0	1.5	0.226	0.877	1.07	0.094	0.939
Median	14.0	3.0	1.26	3.07	3.63	0.198	3.50
Max	14.0	5.0	4.37	10.1	10.5	0.738	7.39
CV%	23	36	76	68	65	61	41
Geometric Mean	n/a	n/a	1.20	3.03	3.51	0.203	3.41
Fasted							
N	19	19	19	19	17	17	17
Mean	13.5	3.8	1.19	4.25	5.05	0.214	4.23
SD	6.18	1.39	1.23	5.07	5.72	0.105	2.35
Min	6.0	2.5	0.150	0.274	0.446	0.075	1.81
Median	14.0	3.5	0.720	1.75	1.96	0.202	3.42
Max	24.0	8.0	4.98	20.1	21.7	0.384	9.29
CV%	46	37	103	119	113	49.2	55.5
Geometric Mean	n/a	n/a	0.718	2.31	2.86	0.188	3.68

AUC = area under the curve; CV = coefficient of variability. No half-life and $AUC_{0\text{-}inf}$ could be calculated for 2 subjects (fasted).
*Approximation.

CIs of all end points are contained within these bounds, the pharmacokinetics of buspirone in T+B after administration under fed and fasted conditions are considered to be equivalent.

Descriptive statistics for both buspirone and 1-PP were calculated separately for each condition. Minimum, median and maximum, mean, SD, and coefficient of variability (CV%) were provided for all PK parameters.

RESULTS

A total of 20 women were enrolled in the study. Demographic characteristics are described in Table 1. One subject was discontinued from the study after the fed condition because of a positive drug test, so a total of 19 subjects completed the fasted condition, and 20 subjects completed the fed condition. For 2 subjects in the fasted condition, no half-life and $AUC_{0\text{-}inf}$ could be calculated.

Pharmacokinetic Results

Buspirone

The mean plasma concentration-time profile of buspirone after administration of T+B is shown in Figure 1.

For buspirone, the 90% CIs of the observed fed/fasted ratios for the plasma $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, and C_{max} after administration of T+B were 102.32–165.97%, 79.60–152.21%, and 126.39–214.58%, respectively (see table 2). None of these ratios were contained within the prespecified bounds of 80% and 125%.

Descriptive statistics are displayed in table 3.

1-(2-pyrimidinyl)piperazine

The mean plasma concentration-time profile of 1-PP after administration of T+B is shown in Figure 2.

Table 4. Summary of pharmacokinetic parameters of 1-(2-pyrimidinyl)piperazine after administration of T+B in healthy female subjects in fed and fasted conditions (primary analysis)

Parameter	Fed		Fasted		Fed/fasted	
	N	LSGM	N	LSGM	Ratio	90% CI
$AUC_{0\text{-}last}$ (hr.ng/ml)	20	27.80	19	25.33	109.76	99.21–121.42
$AUC_{0\text{-}inf}$ (hr.ng/ml)	19	29.58	18	29.63	99.81	91.75–108.59
C_{max} (ng/ml)	20	4.01	19	3.41	117.46	99.85–138.19
*T_{max} (hr)	20	3.25 (1.5–6.0)	19	4.0 (3.0–14.0)		

AUC = area under the curve; LSMG = least-squares geometric mean. No $AUC_{0\text{-}inf}$ could be calculated for 2 subjects (one fed, one fasted).
*Median, minimum and maximum reported for T_{max}.

Table 5. Summary of pharmacokinetic parameters of 1-(2-pyrimidinyl)piperazine after administration of T+B in healthy female subjects in fed and fasted conditions (descriptive statistics)

Treatment	T_{last} (hour)	T_{max} (hour)	C_{max} (ng/mL)	AUC_{last} (h*ng/mL)	$AUC_{0\text{-}inf}$* (h*ng/mL)	λ_z* (1/hour)	$t_{1/2}$* (hour)
Fed							
N	20	20	20	20	19	19	19
Mean	20.5	3.6	4.22	32.9	34.1	0.164	4.70
SD	4.89	1.30	1.32	20.5	22.7	0.052	1.62
Min	14.0	1.5	1.84	10.4	11.3	0.084	2.61
Median	24.0	3.25	4.34	28.3	27.4	0.153	4.54
Max	24.0	6.0	7.18	86.6	103	0.266	8.25
CV%	24	36	31	62	67	32	34
Geometric Mean	19.9	3.35	4.01	27.8	28.8	0.156	4.46
Fasted							
N	19	19	19	19	18	18	18
Mean	19.3	4.7	3.66	29.6	35.7	0.158	4.98
SD	5.13	2.45	1.41	19.1	25.7	0.056	1.87
Min	14.0	3.0	1.26	10.4	10.9	0.080	2.56
Median	24.0	4.0	3.45	19.3	22.5	0.138	5.03
Max	24.0	14.0	6.72	79.8	95.3	0.271	8.63
CV%	27	52	39	65	72	35	38
Geometric Mean	18.6	4.34	3.40	25.0	29.0	0.148	4.67

AUC = area under the curve; CV = coefficient of variability. No half-life and $AUC_{0\text{-}inf}$ could be calculated for 2 subjects (one fed, one fasted).
*Approximation.

The 90% CIs of the observed fed/fasted ratios for the plasma $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, and C_{max} of 1-PP were 99.21−121.42%, 91.75−108.59%, and 99.85−138.19%, respectively (see table 4). All were contained within the prespecified bounds of 80% and 125%, with exception of the upper bound for C_{max}. The mean AUCs and C_{max} for the main (active) metabolite 1-PP did not differ between fed and fasted conditions.

Descriptive statistics are displayed in table 5.

Testosterone and DHT

Plasma concentrations of testosterone and DHT C_{max} and T_{max} did not differ under fed and fasted conditions, which confirms the absence of a possible effect of food on sublingual testosterone absorption. Mean C_{max} and T_{max} of testosterone and DHT are shown in table 6.

Safety

No serious adverse events occurred during the study. 6 participants reported a total of 19 (possible or probable) drug-related treatment-emergent adverse events (TEAEs). In the fed condition, 10 participants reported a total of 14 TEAEs, compared with 6 participants reporting a total of 6 TEAEs in the fasted condition. (Please note that when participants experienced the same TEAE in both conditions, the participant and TEAE were counted as one.) All TEAEs were characterized as mild or moderate, and none led to discontinuation. The most frequently reported complaints were headache, dizziness, and nausea. They were also consistent with those reported for buspirone and/or testosterone use.

DISCUSSION

None of the 90% CIs of the observed fed/fasted ratios of mean plasma $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, and C_{max} for buspirone after administration of T+B were contained within the prespecified bounds. This was especially true for the upper limits; with the exception of $AUC_{0\text{-}inf}$, the lower limits for all fed/fasted ratios were in fact well within these bounds. Moreover, buspirone is extensively metabolized, almost immediately after oral administration, into its main

Table 6. Mean pharmacokinetic parameters of testosterone and dihydrotestosterone

	Testosterone				Dihydrotestosterone			
	C_{max} (ng/ml)		T_{max} (min)		C_{max} (ng/ml)		T_{max} (min)	
	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted
Mean	4.45	5.20	15.0	15.0	0.53	0.62	29.3	29.2
SD	1.32	1.60	0	0	0.18	0.23	3.4	3.4

metabolite 1-PP, resulting in buspirone bioavailability of approximately 4%.[19,24] The 90% CIs of the observed fed/fasted ratios of mean plasma $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} for 1-PP were all contained within the prespecified bounds of 80% and 125%, with the exception of the upper bound for C_{max} (138.19%). Mean AUCs and C_{max} for the 1-PP did not show a statistically significant difference between fed and fasted conditions. This is indicative of adequate systemic exposure to buspirone in both fed and fasted conditions and would justify the conclusion that the small differences in buspirone levels between conditions are not expected to be clinically relevant. Moreover, these differences, such as a slight increase in AUC and C_{max} with food, are in line with conventional formulations of buspirone (see label BuSpar buspirone hydrochloride tablets, United States Pharmacopeial Convention).

The increase in the mean plasma buspirone peak maximum levels after administration of T+B in fed conditions (1.63 ± 1.25 ng/ml) is comparable with previously reported levels of about 2.16 ng/ml (±2.55 ng/ml). In that study, a standard low-calorie breakfast was allowed before administration of T+B,[13] a situation that is highly likely to resemble a potential real-life situation in which the on-demand medication would be taken.

Median T_{max} for buspirone was 3.0 hr in the fed condition and 3.5 hr in the fasted conditions. The median lag time (t_{lag}) was 150 min in the fed condition and 180 min in the fasted condition, indicating a comparable but somewhat faster release in the fed condition. These results are also comparable with the previously reported range of 151−249 minutes, using the same formulation.[13]

In the present study, AUC and C_{max} for buspirone (and 1-PP) are highest in the fed condition. This pattern is normally associated with poorly absorbed active compounds, whereas the opposite is true for readily absorbable compounds such as busprione hydrochloride, due to a delay in, and reduction of, absorption caused by food intake. This reversed pattern was also reported for the testosterone and sildenafil combination tablet.[25] It was hypothesized that, in the fasted condition, lower friction on the delayed-release polymer coating surrounding the tablet's core in the gastrointestinal tract led to sildenafil being released later than in fed conditions. The T+B tablets contain a similar core, which softens as water permeates the polymer coating. The rupture of the core is partly dependent on the aforementioned friction in the gastrointestinal tract, which in turn is dependent on the amount of food present. Therefore, it is likely that buspirone was released earlier and thus more efficiently, in the fed condition.

Finally, it should be noted that the present study could have benefitted from a larger sample size, as it would have enabled a more reliable calculation of the terminal half-life. Another limitation is the lack of differentiation between the enrolled premenopausal and postmenopausal women in the analyses. It is unlikely that the effects of food intake differ in these groups, but based on these results, it cannot be ruled out.

CONCLUSIONS

Administration of T+B after high-caloric food intake slightly increased the bioavailability of buspirone but did not result in differences in T_{max} when compared with fasted conditions. Both in fed and fasted conditions, T+B was generally well tolerated and safe. The slight increase in plasma buspirone exposure observed in fed conditions was comparable with levels reported earlier, as well as with levels reported for conventional buspirone, and is therefore not expected to be clinically relevant. This conclusion is further supported by the similar exposure of 1-PP in fed and fasted conditions and the fact that 1-PP substantially contributes to the pharmacological effects of buspirone. These results, therefore, demonstrate that T+B can safely and effectively be used in both fed and fasted states.

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Corresponding Author: Jeroen Gerritsen, MSc, Emotional Brain B.V., Louis Armstrongweg 88, Almere, 1311 RL, the Netherlands. Tel: +31365468346; Fax: +31365497186; E-mail: j.gerritsen@emotionalbrain.nl

Conflict of Interest: J. Gerritsen, J. Bloemers, K. van Rooij, L. de Leede, R. van der Geest, H.W. Frijlink, H.P.F. Koppeschaar, and A. Tuiten own shares and/or stock options in Emotional Brain in the previous 3 years.

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STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Jeroen Gerritsen; Jos Bloemers; Kim van Rooij; Leo de Leede; Ronald van der Geest; Henderik W. Frijlink; Hans P.F. Koppeschaar; Berend Olivier; Adriaan Tuiten

(b) Acquisition of Data
Jeroen Gerritsen; Jos Bloemers; Kim van Rooij; Hans P.F. Koppeschaar

(c) Analysis and Interpretation of Data
Jos Bloemers; Kim van Rooij; Leo de Leede; Ronald van der Geest

Category 2

(a) Drafting the Article
Jeroen Gerritsen; Jos Bloemers

(b) Revising It for Intellectual Content
Jeroen Gerritsen; Jos Bloemers; Kim van Rooij; Leo de Leede; Ronald van der Geest; Henderik W. Frijlink; Hans P.F. Koppeschaar; Berend Olivier; Adriaan Tuiten

Category 3

(a) Final Approval of the Completed Article
Jeroen Gerritsen; Jos Bloemers; Kim van Rooij; Leo de Leede; Ronald van der Geest; Henderik W. Frijlink; Hans P.F. Koppeschaar; Berend Olivier; Adriaan Tuiten

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