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Pharmacokinetic Properties and Bioequivalence of Two Formulations of Arbidol: An Open-Label, Single-Dose, Randomized-Sequence, Two-Period Crossover Study in Healthy Chinese Male Volunteers

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ABSTRACT

Background: Arbidol is an antiviral drug indicated for the prevention and treatment of all types of influenza infection and some other kinds of acute respiratory infections, specifically against influenza groups A and B, and severe acute respiratory syndrome. It is used to help prevent influenza infection as long as necessary with little risk for influenza mutation rendering it less effective.

Objective: The aim of this study was to compare the pharmacokinetic properties and tolerability, and to determine bioequivalence, of a newly developed generic dispersible tablet formulation (test) and a branded capsule formulation (reference) of arbidol 200 mg in healthy Chinese fasted male volunteers.

Methods: This open-label, single-dose, randomized-sequence, 2-period crossover study was conducted in healthy native Chinese male volunteers. Eligible subjects were randomly assigned in a 1:1 ratio to receive a single 200-mg dose of the test or reference formulation, followed by a 1-week washout period and administration of the alternate formulation. The study drugs were administered after a 12-hour overnight fast. After the study drug administration, serial blood samples were collected for 72 hours after administration. Plasma drug concentrations were determined using high-performance liquid chromatography coupled with tandem mass spectrometry. Several pharmacokinetic parameters, including C_{max}, T_{max}, $t_{1/2}$, AUC_{0-t}, and $AUC_{0-\infty}$, were determined from the plasma concentrations of the 2 formulations of arbidol using noncompartmental analysis. The formulations were to be considered bioequivalent if the log-transformed ratios of C_{max} and AUC were within the predetermined bioequivalence range of 80% to 125% established by the State Food and Drug Administration (SFDA) of the People's Republic of China. Tolerability was assessed by monitoring vital signs (blood pressure, heart rate, temperature, and electrocardiography), laboratory analysis (hematology, blood biochemistry, hepatic function, and urinalysis), and subject interview on adverse events.

Results: Twenty subjects were enrolled and completed the study (mean [SD] age, 21.1 [1.1] years; weight, 64.7 [5.1] kg; and height, 172.3 [3.1] cm). Neither period nor sequence effect was observed. The main pharmacokinetic properties with the test and reference formulations were as follows: C_{max}, 417.4 (107.6) and 414.8 (95.1) ng/mL, respectively (P = NS); median (range) T_{max}, 0.63 (0.25–1.0) and 0.75 (0.5–1.5) hours ($P = 0.035$); AUC_{0-t}, 2033.6 (564.9) and 1992.0 (483.3) ng/mL/h (P = NS); $AUC_{0-\infty}$, 2285.4 (597.7) and 2215.2 (604.0) ng/mL/h (P = NS); and $t_{1/2}$, 6.9 (4.2) and 6.1 (5.2) hours (P = NS). The 90% CIs for the log-transformed ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 91.7% to 109.7%, 91.0% to 112.8%, and 92.0% to 116.3%, respectively (all, $P < 0.05$), which were within the predetermined range for bioequivalence. No adverse events were found on analysis of vital signs or laboratory tests or reported by subjects in this study.

Conclusion: In this study in healthy Chinese male volunteers, the dispersible tablet formulation and the 200-mg capsule formulation of arbidol met the SFDA's regulatory definition of bioequivalence based on the rate and extent of absorption. (*Clin Ther.* 2009;31:784–792) © 2009 Excerpta Medica Inc.

Accepted for publication March 16, 2009.
doi:10.1016/j.clinthera.2009.04.016
0149-2918/$ - see front matter

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Key words: arbidol, bioequivalence, bioavailability, HPLC-MS/MS.

INTRODUCTION

Arbidol is an antiviral drug first marketed in Russia in 1993 and in China in 2006. It is indicated for the prevention and treatment of influenza A and B, respiratory syncytial virus, severe acute respiratory syndrome (including exacerbation of bronchitis and pneumonia), secondary immunodeficiency, overall therapy for chronic bronchitis, pneumonia, and recurrent herpesvirus infections, and for the prevention of postoperative infections and stabilization of immune status.[1–5] Arbidol might prevent contact and entry of viruses into cells by inhibiting the fusion of viral lipid membranes with cell membranes. It has also been reported that arbidol has interferon-inducing activity, activated phagocytic activity of macrophages, and stimulated humoral and cell-mediated immunity, and that it heightens the body's ability to fight infection.[6–10]

T_{max} with a single 50-mg dose of arbidol has been reported to be 1.2 hours; with 100 mg, 1.5 hours. Arbidol is metabolized in the liver. The $t_{1/2}$ of the drug in the body is 17 to 21 hours. Approximately 40% is excreted unchanged, mostly (38.9%) through the bile, with an insignificant amount (0.12%) excreted through the kidneys. Within the first 24 hours after administration, 90% of the drug has left the body.[11]

The aim of the present study was to compare the pharmacokinetic properties and determine bioequivalence of two 200-mg formulations of arbidol: a newly developed generic formulation (dispersible tablet; test) and a branded capsule formulation (reference) in healthy Chinese fasted male volunteers.

SUBJECTS AND METHODS

Study Design and Subject Selection

This open-label, single-dose, randomized-sequence, 2-period crossover study was conducted at the First Affiliated Hospital of China Medical University, Shenyang, People's Republic of China. The study was conducted according to the principles of the Declaration of Helsinki and its amendments[12] for biomedical research involving human subjects and the principles of the Good Clinical Practice guideline.[13] The clinical protocol and the informed-consent form were approved by the local ethics committees at China Medical University.

Healthy Chinese male nonsmoking volunteers were selected for this study. All subjects signed an informed-consent form after they were given the detailed information about the aims, restrictions, and adverse events that could be experienced as a result of receiving the study drug. Before study entry, subjects underwent an interview regarding their occupation, smoking and drinking habits, and medical history; routine physical examination, including vital sign monitoring (blood pressure, heart rate, temperature, and electrocardiography); and laboratory analysis (ie, hematology, blood biochemistry, hepatic function, and urinalysis) to ensure that they were healthy enough to take part in the study.

Subjects who had a history or evidence of a renal, gastrointestinal, hepatic, or hematologic abnormality; any acute or chronic disease; or an allergy to any chemicals were excluded. Subjects who had used drugs of any kind within the 2 weeks prior to the start of or during the study were excluded, as were those with alcohol abuse (>28 U of alcohol per week [1 U = 285 mL of beer]).

Study Drug Administration

Enrolled subjects were randomized in a 1:1 ratio, using a table of random numbers, to receive a single 200-mg dose of arbidol as a dispersible tablet (test) formulation* (lot no. 20050901; expiration date, September 2007) followed by a capsule (reference) formulation† (lot no. 050701; expiration date, June 2007), or vice versa. Subjects were hospitalized at 8 PM and given a standardized evening meal (200–~400 g of cooked rice or other staple food, ~400 g of vegetables, ~50 g of meat, and 250 mL of water). At 7 AM after an overnight fast (as required by the State Food and Drug Administration [SFDA] of the People's Republic of China), subjects were administered a single 200-mg dose of arbidol (test or reference formulation) with 250 mL of water and then fasted for 4 hours. A standardized lunch (the same as the standardized evening meal) and a standardized evening meal were served at 4 and 9 hours, respectively, after study drug administration. No other food was permitted during the period; water was available 2 hours after study drug administration.

*Manufactured by Chengdu Open Pharmaceutical Co. Ltd., Chengdu, People's Republic of China.

†Trademark: En Er Xin® (Shijiazhuang No. 4 Pharmaceutical Co. Ltd., Shijiazhuang, People's Republic of China).

After a 1-week washout period, subjects returned to the clinical unit, where the alternative formulation was administered and blood samples were drawn as before so as to complete the crossover design.

Blood Sample Collection

In this study, blood samples (5 mL) were collected from a suitable forearm vein using an indwelling catheter into heparin-containing tubes before (0 hour; baseline) and 0.125, 0.25, 0.5, 0.75, 1.0, 1.5, 2, 4, 7, 12, 24, 48, and 72 hours after study drug administration. Just before each blood sample was collected, heparin in the heparin-locked catheter was discarded with 0.5 mL of blood. All of the blood samples were immediately centrifuged at 1000*g* for 10 minutes at room temperature (20°C) for separating plasma, and plasma samples were stored at –20°C until quantitative analysis for the determination of plasma arbidol concentrations. The sample collection and handling processes were protected from sunlight.

Determination of Plasma Arbidol Concentrations

A method of the determination of arbidol concentration in plasma using high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS) was used and has been described elsewhere.[14,15]

Chemicals and Materials

Arbidol hydrochloride and diazepam (as the internal standard [IS]) were obtained from the National Institute for the Control of Pharmaceutical and Biological Products, Beijing, People's Republic of China (purity >99.5%). The deionized water was purified using the Milli-Q water system (Millipore Research and Development, Bedford, Massachusetts). Methanol (Merck KGaA, Darmstadt, Germany) was of high-performance LC grade. Formic acid (Tedia Co., Inc., Fairfield, Ohio), sodium carbonate (Na_2CO_3, Shandong Aona Chemical Co. Ltd., Liuyuan, People's Republic of China), and diethyl ether (Sigma-Aldrich Corporation, St. Louis, Missouri), were all of analytical grade and commercially available. Blank plasma was obtained from a blood center in Shenyang, People's Republic of China.

HPLC-MS/MS Conditions

An HPLC-MS/MS 2010A System (Shimadzu Corporation, Tokyo, Japan) was used, and separation was achieved on a C_{18} column (100 × 2.0-mm internal diameter [ID], 3-µm particle size, Shiseido Co., Ltd., Tokyo, Japan), which was preceded by the use of a guard column (C_{18}, 10 × 4.6-mm ID, Phenomenex, Inc., Torrance, California) at a column temperature of 20°C. The mobile phase was prepared by mixing methanol:5% formic acid at a ratio of 72:28 (vol/vol), an injection volume of 2 µL, and a flow rate of 0.3 mL/min. Separation was conducted under isocratic conditions, and the total running time was within 3 minutes.

The electrospray ionization source was performed in the selected ion monitoring mode. The $[M + H^+]$, m/z 479 for arbidol, and the $[M + H^+]$, m/z 286 for the IS, using diazepam as the IS, were selected as detecting ions, respectively. The MS operating conditions were optimized as follows: drying gas (nitrogen gas), 2.0 L/min; curved desolvation line temperature, 250°C; atomization gas (nitrogen gas), 1.5 L/min; and detector voltage, 1.4 kV. Analytical data were processed using HPLC-MS/MS Solution 3.0 (Shimadzu Biotech, Nakagyo-ku, Japan), and the peak area was used for quantification.

Sample Preparation

Frozen human plasma samples were thawed at ambient temperature. Plasma samples (500 µL) were spiked with 50 µL of IS (diazepam 10 µg/mL), 50 µL of methanol, 400 µL of 0.04-mol/L Na_2CO_3, and 3 mL of diethyl ether and vortex-mixed for 3 minutes. After centrifugation (2000*g*, 4°C, 5 minutes), the organic phase was transferred to another dry clean tube and evaporated to dryness in a thermostatically controlled water-bath at 40°C in a slight stream of nitrogen. The residue was dissolved in 100 µL of methanol, with 2 µL used for HPLC-MS/MS analysis. Sample extraction was protected from light.

Method Validation and Quantification

To investigate the specificity and selectivity of the HPLC-MS/MS method, blank human plasma samples, spiked plasma samples, and subject samples were prepared and analyzed. Chromatography findings are shown in **Figure 1**. The arbidol and diazepam retention times were 1.7 and 2.8 minutes, respectively, suggesting that no endogenous peaks at the retention time of arbidol and IS interfered with the determination.

The calibration curves of arbidol in human plasma were obtained using 6 calibration standards, each of which was prepared in triplicate and extracted together with blank samples and quality control (QC)

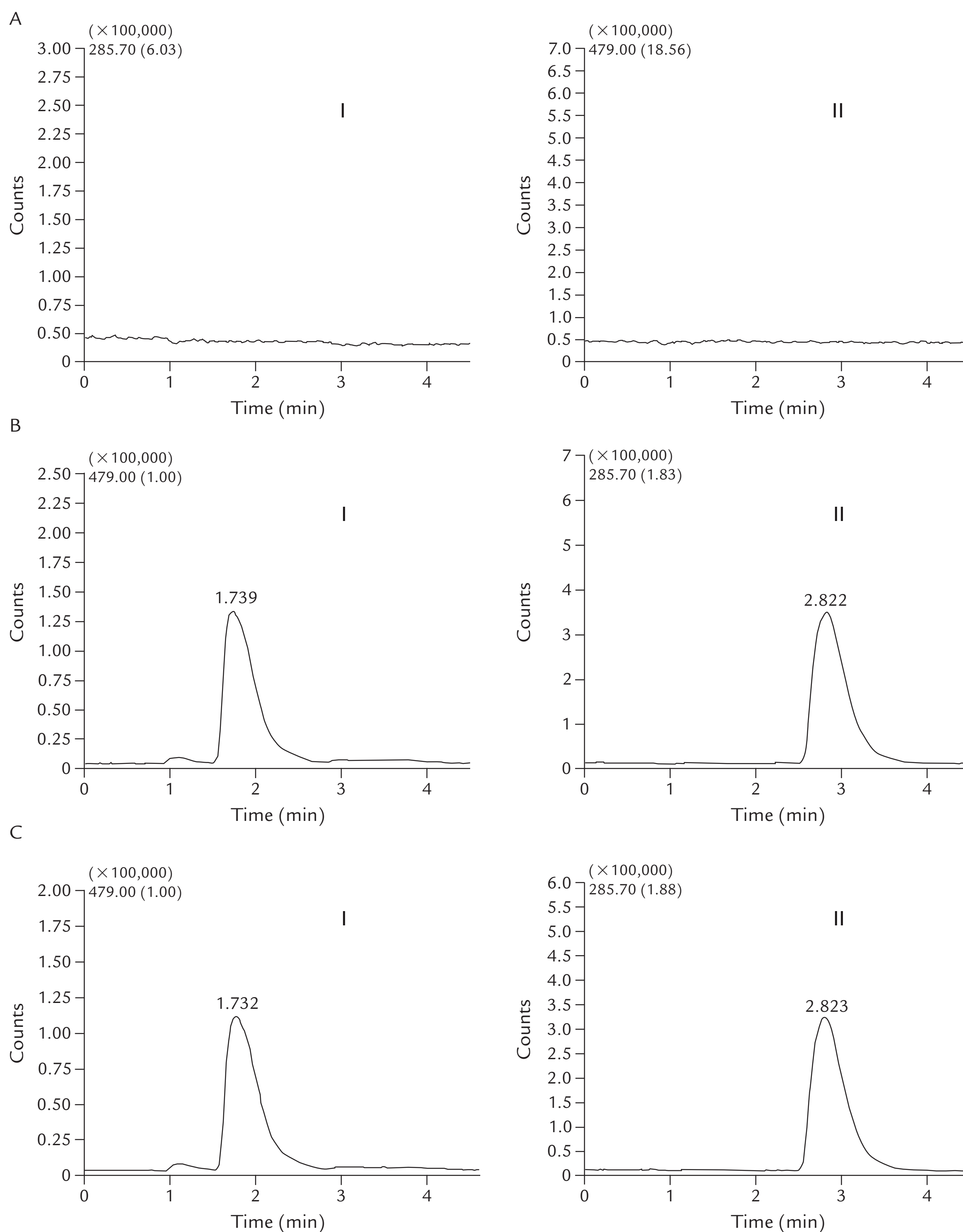

Figure 1. High-performance liquid chromatography/tandem mass spectrometry of (A) blank plasma, (B) plasma spiked with 800-ng/mL arbidol and 10-µg/mL diazepam (internal standard), and (C) plasma sample of a healthy Chinese male subject obtained 0.5 hour after single-dose administration of 200-mg arbidol hydrochloride dispersible tablet (manufactured by Chengdu Open Pharmaceutical Co., Ltd., Chengdu, People's Republic of China). Peak I = arbidol; peak II = diazepam.

samples. The peak area was used for quantification. QC samples were used to assess the intraday and interday precision, accuracy, and recovery, prepared by spiking control human plasma with 10-, 25-, 100-, 200-, 500-, and 1000-ng/mL arbidol. The linearity was observed within the range of 10 to 1000 ng/mL, with a correlation coefficient <0.9965 (n = 6). The lower limit of quantification of arbidol was 10 ng/mL.

The intraday and interday variations and recoveries for arbidol determination in human plasma are shown in **Table I**.

The short-term stability of extracted arbidol samples for 24 hours at room temperature and the freeze–thaw cycles stability of frozen samples (frozen at –20°C, thawed at room temperature [20°C], freeze–thaw for 3 cycles, 2 hours per cycle) were determined to ensure that the samples were stable during the handling and analysis processes. Long-term storage stability of plasma samples at –20°C was determined after 45 days to ensure that the stability of frozen samples at storage temperature (–20°C) could not affect reliability of the results on HPLC-MS/MS analysis. The results of the stability of arbidol in the human plasma (freeze–thaw for 3 cycles and short-term stability) and long-term storage (–20°C, 45 days) are shown in **Table II**. Arbidol was stable for 24 hours at room temperature (20°C) in extracted plasma samples, for 45 days at –20°C, and within 3 freeze–thaw cycles in plasma samples.

The analytical method for arbidol quantification in plasma samples was validated and applied to the bioequivalence study according to the international guidelines.[16,17]

Tolerability

The investigators included 2 clinicians, a clinical pharmacist, and ≥2 nurses who monitored the subjects for adverse events. These events were also determined using subject interview (subjective chief complaints by subjects, objective observation by clinicians) regarding the potential presence of adverse events, such as allergic reaction, nausea, diarrhea, and dizziness[18,19] at any time during the study, and by comparing the results of vital signs monitoring (blood pressure, heart rate, and body temperature) and laboratory tests (hematology, blood biochemistry, hepatic function, and urinalysis) at baseline, 12 hours after study drug administration, 7 days after completion of the study (follow-up visit), and for 6 additional months thereafter (self-report by subjects).

Pharmacokinetic and Statistical Analyses

Pharmacokinetic analysis was performed by using DAS version 2.0, authorized by the Chinese Pharmacology Society, Beijing, People's Republic of China. Data obtained from individual volunteers were subjected to noncompartmental pharmacokinetic analysis.[16,17,20] AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, and elimination rate constant (k_e) were determined in each volunteer. C_{max} and T_{max} were obtained directly from the observed data. k_e was obtained as the slope of the linear regression of the log-transformed concentration versus time

Table I. Intraday and interday variations and recoveries for determination of arbidol in human plasma. Values are mean (SD) unless otherwise specified.

Spiked Concentration, ng/mL	Intraday			Interday			Recovery, %	
	True Concentration, ng/mL	RSD, % (n = 6)	RE, %	True Concentration, ng/mL	RSD, % (n = 6)	RE, %	Absolute	Relative
25	24.3 (0.9)	3.6	–3.0	23.8 (1.2)	5.2	–4.8	69.3 (4.3)	97.0 (3.5)
200	197.4 (12.2)	6.2	–1.3	191.9 (12.4)	6.4	–4.1	76.8 (7.8)	98.7 (6.1)
800	801.5 (54.6)	6.8	0.1	803.9 (58.2)	7.2	0.5	73.4 (6.9)	100.1 (6.8)

RSD, % = relative SD, calculated as SD/Mean × 100%; RE, % = relative error, calculated as (True concentration – Spiked concentration)/Spiked concentration × 100%.

Table II. Stability data for arbidol in human plasma (n = 6).* Values are mean (SD).

Stability	Spiked Concentration, ng/mL		
	25	200	800
Short-term stability			
Baseline	25.3 (1.8)	187.0 (6.1)	800.9 (52.9)
After 24 h at room temperature	25.8 (1.0)	193.3 (5.5)	791.1 (54.5)
Long-term stability			
Baseline	23.9 (2.7)	175.1 (9.6)	905.8 (9.4)
After 45 d at –20°C	25.4 (2.2)	193.2 (28.2)	904.2 (7.2)
Freeze–thaw stability			
Baseline	21.7 (0.3)	180.2 (1.6)	867.9 (3.1)
After 3 freeze–thaw cycles†	22.4 (0.6)	179.6 (0.8)	887.8 (8.8)

*No significant differences versus baseline were found.
†Freeze temperature, –20°C; thaw temperature, room temperature (20°C); 2 hours for each cycle.

data in the terminal portion of the curve. $t_{1/2}$ was calculated as 0.693/k_e. AUC_{0-t} was calculated according to the trapezoidal rule. $AUC_{0-\infty}$ was calculated using the following formula[16]:

$$AUC_{0-\infty} = AUC_{0-t} + C_t/k_e,$$

where C_t was the last measurable concentration.

To test the bioequivalence of the test and reference formulations, analysis of variance (ANOVA) for the crossover design was conducted on log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. The ratios of the log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were calculated using the *F* score. The probability of exceeding the limits of acceptance for bioequivalence established by the SFDA (80%–125%) was obtained using two 1-sided *t* tests, as described by Schuirmann[21] and the US Food and Drug Administration.[22] The formulations were to be considered bioequivalent if the log-transformed ratios (test/reference) of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the predetermined bioequivalence range of 80% to 125% and if *P* was <0.05 for the 90% CIs.[21,22]

RESULTS

A total of 20 subjects (mean [SD] age, 21.1 [1.1] years [range, 20–25 years]; weight, 64.7 [5.1] kg [range, 57–75 kg]; height, 172.3 [3.1] cm [range, 165–180 cm]) were enrolled in the study. All subjects completed both treatment periods, with no protocol violations. No abnormalities were found in clinical or biochemical parameters on comparison of baseline versus end-of-study assessments.

Pharmacokinetic Properties

The mean (SD) pharmacokinetic values for the test and reference formulations, respectively, were as follows: C_{max}, 417.4 (107.6) and 414.8 (95.1) ng/mL (*P* = NS); median (range) T_{max}, 0.63 (0.25–1.0) and 0.75 (0.5–1.5) hours (*P* = 0.035); AUC_{0-t}, 2033.6 (564.9) and 1992.0 (483.3) ng/mL/h (*P* = NS); $AUC_{0-\infty}$, 2285.4 (597.7) and 2215.2 (604.0) ng/mL/h (*P* = NS); and $t_{1/2}$, 6.9 (4.2) and 6.1 (5.2) hours (*P* = NS). No period or sequence effects were detected for the pharmacokinetic properties on ANOVA. The pharmacokinetic properties of the test and reference formulations are summarized in **Table III**. There were no significant differences between the test and reference formulations in AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, or $t_{1/2}$ by paired *t* test, with the exception of T_{max} by Wilcoxon signed rank test.

The mean plasma concentration–time profiles of the 2 formulations after administration of a single oral dose of 200-mg arbidol are shown in **Figure 2**. The 90% CIs of the ratios (test/reference) for the log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ values, as well

Table III. Pharmacokinetic parameters of 2 oral formulations (dispersible tablet [test]* and capsule [reference]†) of arbidol after a single 200-mg administration in healthy Chinese male volunteers (N = 20). Values are mean (SD) unless otherwise specified.

Parameter	Test	Reference	*P*
C_{max}, ng/mL	417.4 (107.6)	414.8 (95.1)	0.900
T_{max}, h, median (range)	0.63 (0.25–1.0)	0.75 (0.5–1.5)	0.035
$t_{1/2}$, h	6.9 (4.2)	6.1 (5.2)	0.580
AUC_{0-t}, ng/mL/h	2033.6 (564.9)	1992.0 (483.3)	0.730
$AUC_{0-\infty}$, ng/mL/h	2285.4 (597.7)	2215.2 (604.0)	0.638

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as the probability of exceeding the limits of acceptance for bioavailability and the power of the test are shown in **Table IV**. The 90% CIs for the ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 91.7% to 109.7%, 91.0% to 112.8%, and 92.0% to 116.3%, respectively, which were within the range of 80% to 125%. All *P* values were <0.05.

Tolerability

No adverse events were observed by clinicians, found on the analyses of vital sign monitoring or laboratory analysis, or reported by subjects during or after the study.

DISCUSSION

The findings from the present study with regard to T_{max} and $t_{1/2}$ (~0.63 and ~6 hours, respectively) were consistent with those from a review by Liu et al,[15] who reported that the T_{max} of arbidol was ~40 minutes, and $t_{1/2}$ was ~7.5 hours after study drug administration. Glushkov[11] had reported that T_{max} was 1.2 hours after the administration of a 50-mg dose, T_{max} was 1.5 hours after the administration of a 100-mg dose, and $t_{1/2}$ was 17 to 21 hours. The product information of the arbidol capsule formulation[19] mentions that T_{max} was 1.63 hours and $t_{1/2}$ was ~11 to 17 hours.

The comparison of our findings with those from previously published studies suggests that the rate and extent of absorption were different between the dispersible tablet and capsule formulations, and the elimination rate was different between Russian and Chinese populations. The different k_e results might have been related to the differences between the races of the studied populations. In the present study, the T_{max} of the test formulation was significantly shorter compared with that of the reference formulation ($P < 0.05$). This finding might have been the result of differences in the preparation technologies between the tablet (test) and capsule (reference) formulations. The results would be instructive for administration in patients in the different states of illness in clinical practice.

The present study had a few limitations that should be considered. First was the small sample size; single-dose, open-label design; and assessment of clinical relevance of the adverse events by the investigators. The pharmacokinetic data in this study were obtained only from healthy Chinese male volunteers; the pharmacokinetic properties of arbidol might be different in women and in infected patients in clinical practice. Because this study was conducted in fasted subjects, the results cannot be applied to predict the pharmacokinetic properties of arbidol concurrently administered with food. The methods used for the assessment of the tolerability were not perfect, and the sample size was not large enough to observe all of the possible adverse events. The sample size, 20 volunteers, is typical in bioequivalence studies according to the SFDA guideline.[16] However, a larger sample size may be needed to assess tolerability and to represent pharmacokinetic properties in the Chinese population in future studies.

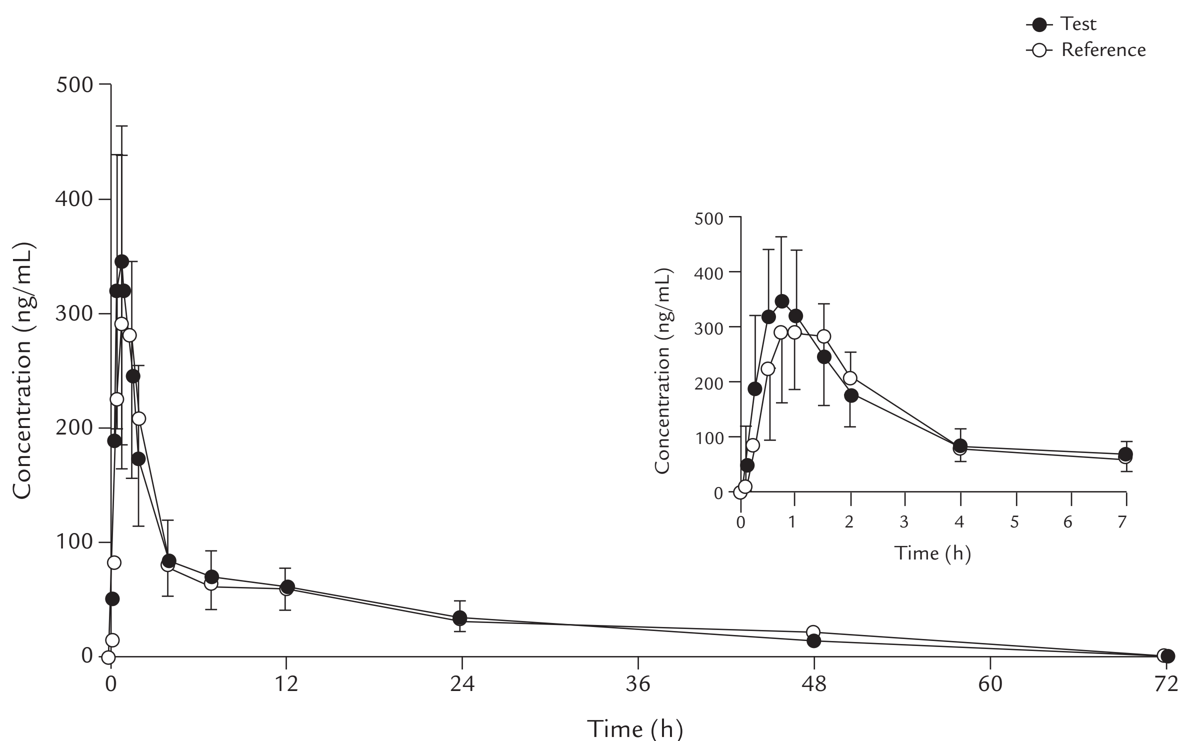

Figure 2. Mean (SD) plasma concentration–time profiles of 2 oral formulations (dispersible tablet [test; manufactured by Chengdu Open Pharmaceutical Co., Ltd., Chengdu, People's Republic of China] and capsule [reference; trademark: En Er Xin® (Shijiazhuang No. 4 Pharmaceutical Co. Ltd., Shijiazhuang, People's Republic of China]) of arbidol after a single 200-mg administration in healthy Chinese male volunteers (N = 20). Inset shows detail of hours 0 to 7 after study drug administration.

Table IV. Comparison of 90% CIs for the log-transformed ratios of pharmacokinetic parameters of 2 oral formulations (dispersible tablet [test]* and capsule [reference]†) of arbidol after a single 200-mg administration in healthy Chinese male volunteers (N = 20).

Parameter	Test: Reference Ratio, %	90% CI	*P* for Exceeding Limits of Acceptance		Power
			<80%	>125%	
C_{max}, ng/mL	102.7	91.7–109.7	<0.001	<0.001	0.99
AUC_{0-t}, ng/mL/h	105.0	91.0–112.8	<0.001	<0.001	0.99
$AUC_{0-\infty}$, ng/mL/h	108.0	92.0–116.3	<0.001	<0.005	0.99

*Manufactured by Chengdu Open Pharmaceutical Co., Ltd., Chengdu, People's Republic of China.
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CONCLUSION

In this small study in healthy Chinese fasted male volunteers, single 200-mg doses of the arbidol dispersible tablet (test) and capsule (reference) formulations met the SFDA regulatory definition of bioequivalence based on the rate and extent of absorption.

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