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Evaluation of the Bioequivalence of Acarbose in Healthy Chinese People

Yan Chen, Fahao Guo, Xin Wang, LuYao Liu, Can Yang, YuQing Xiong, and Hong Zhang

Abstract

The purpose of this study was to determine whether the reference formulation and test formulation of acarbose are bioequivalent among healthy Chinese subjects based on evaluation of the pharmacodynamic end point. Two clinical trials with acarbose were conducted: study A, a pilot study (n = 12; 50 and 100 mg), and study B, a pivotal study (n = 60; 50 mg). In study A, there was a dose-dependent relationship between 50 mg acarbose and 100 mg acarbose and a significant difference compared with sucrose alone. In study B, after logarithmic conversion, a linear mixed-effects model was used to analyze the maximum serum glucose value and area under the serum glucose-time curve from 0 to 2 hours. The geometric mean ratios (test formulation/reference formulation) were 92.68% and 95.70%, with 90% confidence intervals of 84.08%-102.17% and 84.21%-108.76%, respectively, falling between 80.00% and 125.00%. According to the geometric least-squares mean, the test formulation (or reference formulation) was statistically significantly different as a single sucrose ($P < .001$). The effective dose of acarbose in healthy Chinese volunteers was 50 mg. The reference and test formulations were bioequivalent.

Keywords

acarbose, bioequivalence, effective dose, healthy Chinese people, pharmacodynamic

Type 2 diabetes is a common chronic disease that is closely related to people's lifestyles and diet. In recent years, in the context of rapid social and economic development, the incidence of type 2 diabetes has trended toward increasing annually, greatly impacting people's quality of life and health.[1] With the exception of some patients in whom type 2 diabetes can be controlled with diet therapy and exercise therapy, medications are required. At present, sulfonylureas, biguanides, glucosidase inhibitors, and other drugs are mostly used in clinical treatment. Glucosidase inhibitors have been increasingly used in Asia, where carbohydrates are the main diet. Acarbose is a representative glucosidase inhibitor.[2–4] Acarbose is a pseudotetrasaccharide with a structure that is very similar to oligosaccharides; it competitively and reversibly inhibits α-glucosidase of the brush border of the small intestine and blocks the degradation of starch and sucrose.[5,6] It also delays the absorption of glucose and fructose in the digestive tract, thereby delaying and reducing the increase in serum glucose after a meal, balancing the absorption of glucose from the intestine, reducing the fluctuation of serum glucose throughout the day and keeping serum glucose in a good state.[6,7] The bioavailability of acarbose is extremely low, and drugs or active metabolites are not detectable in human plasma. The inability to evaluate the pharmacokinetics (PK) after oral acarbose means that the acarbose bioequivalence (BE) test cannot be based on PK end points. Therefore, it is recommended that pharmacodynamic (PD) end points be used for BE evaluation.[8,9]

Previous BE studies on acarbose have mainly used methods recommended by the US Food and Drug Administration.[9,10] One study used a single-administration, 2-cycle self-crossover method, and blood was collected in 0-4 hours.[10] This study showed that more than 30% of PD parameters in subjects had negative values, so the data from these subjects could

Clinical Pharmacology Institute, Nanchang University, Nanchang, P. R. China

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Corresponding Author:
Hong Zhang, PhD, Clinical Pharmacology Institute, Nanchang University, Xuefu Road 1299#, Nanchang, 330006, P. R. China
(e-mail: zh2003nc@163.com)

not be counted. This can be attributed to the homeostatic control of glucose concentration. Similarly, in this study,[9] it was found that regardless of whether acarbose was given, the serum glucose level increased and returned to baseline about 2 hours after taking the drug. Both studies showed that acarbose had high variability in healthy subjects. According to the evaluation of the PD parameters, a large number of subjects were required to meet the conventional regulatory BE criteria (80.00% to 125.00%).[9,10]

To avoid the above 2 scenarios of many negative values of PD parameters requiring a large number of subjects, we adopted the rectifying method proposed by the scholars of Sungkyunkwan University (Seoul, South Korea).[11] The design is a placebo-controlled crossover (3 × 3) method. According to the recommendations of that study[11] and others,[9,10] we shortened the sampling time from 0-4 hours to 0-2 hours. After administration, the maximum serum glucose value (C_{max}) after subtracting the zero-point baseline and area under the serum glucose-time curve from 0 to 2 hours ($AUC_{0–2h}$) obtained by subtracting the zero-point baseline were used as the main PD parameters for evaluation. These 2 PD parameters better reflect the hypoglycemic effect of acarbose on the increase in serum glucose caused by sucrose can also distinguish the difference between different doses of acarbose, and meets the BE requirements.

Materials and Methods

Drugs

The reference formulation (R) was Glucobay 50 mg, Batch No. BJ45279 (Bayer Pharma AG, Wuppertal, Germany); and the test formulation (T) was acarbose tablets 50 mg, Batch No. 1120180502 (China Resources SECCO Pharmaceuticals Co., Ltd., Tokyo, Japan).

Subjects

For the 2 studies, eligible subjects were selected from healthy Chinese volunteers aged ≥ 18 years. Female body weight was ≥45 kg, and male body weight was ≥50 kg, and body mass index (BMI) was between 19 and 24 kg/m^2. All subjects underwent a medical examination including a physical examination, medical history, vital sign determination, and laboratory examination. The exclusion criteria were: fasting serum glucose > 6.10 mmol/L or serum glucose > 7.80 mmol/L 2 hours after a meal; history of drug and food allergies; history of drug abuse or a positive urine drug screening result; history of alcoholism or positive result of alcohol breath test; or history of blood donation or participation in another clinical trial within 3 months prior. The trial was approved by the Ethics Committee of Pingxiang People's Hospital (Pingxiang, China). All subjects in the study fully understood the risks and benefits of this clinical trial and provided written informed consent.

Study Design

The clinical trials were divided into a pilot trial (study A) and pivotal trial (study B). The purpose of study A was to determine the effective dose of acarbose. In study B, the effective dose of acarbose was used to determine whether the reference preparation and test preparation were bioequivalent. Study A was a randomized, open, 3-period, 3 × 3 crossover clinical trial study with 12 eligible subjects. The subjects were randomly divided into 3 groups, and the trial was conducted in 3 cycles. After each cycle, 150 mL of sucrose water was administered. In each cycle, the subjects randomly received 1 of the following 3 treatments (Table 1): 50 mg R, 100 mg R, or only 100 mL of water. To reduce the difference between periods and the statistical results are more reasonable.

Study B was a randomized, open, controlled, 3-period, double 3 × 3 Latin design BE study with 60 eligible subjects. The subjects were randomly divided into 6 groups, and the trial was conducted in 3 cycles. After each cycle, 150 mL of sucrose water was administered. The subjects received 50 mg R, 50 mg T, or 100 mL of water.

Clinical Trial Process and Sample Collection

Eligible subjects arrived at the clinical trial center the morning before drug administration. After admission, the subjects received a unified standard diet and did not exercise vigorously or lie flat for long periods. On the day of each cycle of dosing, according to the dosing schedule, medicine was taken with warm water 10 minutes before sucrose water was taken. In the sucrose alone group, warm water was taken before sucrose water. The subjects were fasted for at least 10 hours overnight the day before drug administration. Drinking water was prohibited 1 hours before drug administration to 1 hour after sucrose water was taken. A subject's water was kept upright from the end of the administration to the end of blood collection. The washout period of this study was 7 days. There were 12 blood collection points per cycle 0 minutes before taking the drug and 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, and 120 minutes after taking sucrose water. About 4 mL of venous blood was collected each time, allowed to stand for at least 30 minutes before centrifugation for 10 minutes at 2°C-8°C (1300 rpm).

PD and BE Analysis

The PD end points for this study were C_{max} and $AUC_{0\text{-}2h}$. The mean C_{max} was obtained by deducting the zero baseline from the maximum serum glucose value (the negative value was zero), and the mean $AUC_{0\text{-}2h}$

Table 1. Drug Administration Summary Table

Study	Grouping and Sequence	n	First Cycle	Second Cycle	Third Cycle
Study A	1	4	Sucrose	Sucrose + 50 mg R	Sucrose + 100 mg R
	2	4	Sucrose + 50 mg R	Sucrose + 100 mg R	Sucrose
	3	4	Sucrose + 100 mg R	Sucrose	Sucrose + 50 mg R
Study B	1	10	Sucrose	Sucrose + 50 mg R	Sucrose + 50 mg T
	2	10	Sucrose + 50 mg R	Sucrose + 50 mg T	Sucrose
	3	10	Sucrose + 50 mg T	Sucrose	Sucrose + 50 mg R
	4	10	Sucrose	Sucrose + 50 mg T	Sucrose + 50 mg R
	5	10	Sucrose + 50 mg T	Sucrose + 50 mg R	Sucrose
	6	10	Sucrose + 50 mg R	Sucrose	Sucrose + 50 mg T

was the area under the 0- to 2-hour serum glucose-time curve obtained after subtracting the zero baseline (negative value was zero). The full analysis set (FAS) included all subjects who were randomized and received acarbose. The PD parameter end point (PD parameter set [PDPS]) was used to calculate the C_{max} and $AUC_{0\text{-}2h}$. Simultaneously, the mean, standard deviation, coefficient of variation, quartile, maximum, minimum, and geometric mean of each parameter were calculated. The PDPS included subjects who obtained a PD parameter data set among subjects who had received at least 1 study drug. BE analysis used a BE set (BES), and a linear mixed-effects model was used to calculate the 90% confidence interval (CI) of the log-transformed geometric mean ratio (test formulation/reference formulation) of the C_{max} and $AUC_{0\text{-}2h}$ and compare the equivalence. At the same time, the difference was compared among the test formulation, reference formulation, and sucrose alone. BES subjects include at least 1 cycle and had a statistical analysis set of evaluable PK parameters.

Detection Method of Serum Glucose Concentration

The concentration of serum glucose was determined by the hexokinase method, using the AU 480 series biochemical analyzer (Beckman Coulter, Sykesville, Maryland), as previously described.[12,13] The principle of this detection method is that in the presence of adenosine triphosphate and magnesium ions, glucose is phosphorylated by hexokinase to produce 6-phosphate glucose and adenosine diphosphate. Glucose 6-phosphate dehydrogenase specifically oxidizes glucose 6-phosphate to 6-phosphogluconate, whereas NAD+ is reduced to NADH. The increase in absorbance at 340 nm is directly proportional to the glucose concentration in the sample. The analysis range of this analytical method is 180-8100 μg /mL, and the correlation coefficient is 0.9999. The low quality control (LQC) and high quality control (HQC) of the intra-assay precision were both 0.7%, and the LQC and HQC of interassay precision was 1.5% and 1.0%, respectively. Accuracy was −7.4% to 5.6%. The stability of QC samples included storage at room temperature for 24 hours, stored in a refrigerator below −60°C for 90 days, and freeze-thawed cycle 5 times below −60°C; all the relative errors of stability under all conditions were within ±10%.

Results

Study A

A total of 39 subjects were screened in study A, 12 of whom met the inclusion criteria. These 12 subjects all completed the trial and were all included in the FAS, PDPS, and BES. The demographic data of these 12 subjects are shown in Table 2. In study A, among the 12 healthy subjects (5 men and 7 women), average age was 28.0 ± 8.3 years, weight was 55.4 ± 6.8 kg, height was 162 ± 8.0 cm, and BMI was 21.1 ± 1.4 kg/m^2. WinNonlin 8.1 software was used to calculate the PD parameters of acarbose. The PK parameters of 12 subjects who met the PDPS by oral acarbose tablets are shown in Table 3. After fasting single oral of sucrose alone, 50 mg acarbose-sucrose, and 100 mg acarbose-sucrose, blood sugar C_{max} was 64.6 ± 15.7, 32.0 ± 13.0, and 22.9 ± 14.0 mg/100 mL, respectively, and blood sugar $AUC_{0\text{-}2h}$ was 61.5 ± 20.0, 27.2 ± 13.0, and 22.4 ± 13.4 mg·h/100 mL, respectively. Twelve subjects had an average serum glucose concentration-time graph after single oral drug + sucrose or single sucrose (Figure 1). Compared with the sucrose alone group, 50 or 100 mg acarbose had statistical significance in reducing blood sugar ($P < .001$; Table 4). After logarithmic transformation of the C_{max} and $AUC_{0\text{-}2h}$ in healthy subjects taking sucrose alone or drug + sucrose in a single oral administration, the geometric least-squares mean was calculated ($P < .001$; Table 5). The results of logarithm conversion analysis of the serum glucose concentration before administration of sucrose alone and drug + sucrose showed that the $P > .05$, indicating that there was no statistically significant difference in the serum glucose concentration before administration of sucrose alone and drug + sucrose. The C_{max} and $AUC_{0\text{-}2h}$ of sucrose alone and

Table 2. PDPS Analysis of Healthy Subjects After Fasting — Single Oral Drug + Sucrose or Single Sucrose

Study	Group	C_{max} (mg/100 mL)	$AUC_{0\text{-}2h}$ (mg·h/100 mL)
Study A	Sucrose (mean ± SD)	64.6 ± 15.7	61.5 ± 20.0
	Sucrose + 50 mg R (mean ± SD)	32.0 ± 13.0	27.2 ± 13.0
	Sucrose + 100 mg R (mean ± SD)	22.9 ± 14.0	22.4 ± 13.4
Study B	Sucrose (mean ± SD)	61.4 ± 18.0	61.6 ± 27.2
	Sucrose + 50 mg R (mean ± SD)	31.7 ± 13.9	31.8 ± 18.8
	Sucrose + 50 mg T (mean ± SD)	29.2 ± 12.4	29.7 ± 15.2

$AUC_{0\text{-}2h}$, area under the serum glucose-time curve obtained after deducting the zero baseline; C_{max}, maximum value of serum glucose after deducting the zero baseline; SD, standard deviation.

Table 3. Demographic Characteristics of Subjects

Demographics	Study A (n = 12)	Study B (n = 59)
Male/Female (n)	5/7	31/28
Age (years)	28.0 ± 8.3	27.5 ± 6.6
Height (cm)	162.0 ± 8.0	162.7 ± 7.8
Weight (kg)	55.4 ± 6.8	57.7 ± 7.4
BMI (kg/m^2)	21.1 ± 1.4	21.7 ± 1.4

BMI, body mass index.

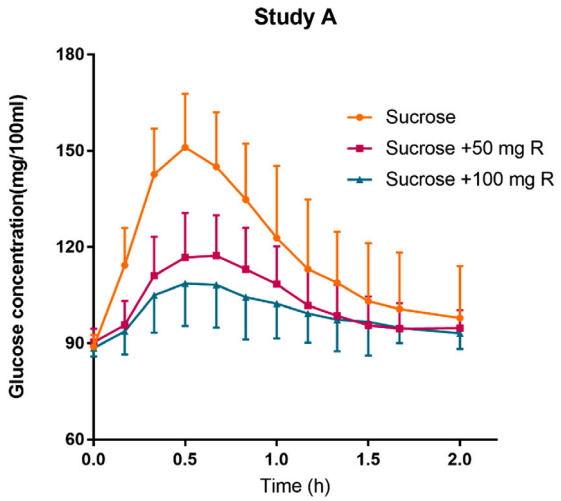

Figure 1. Mean serum glucose concentration-versus-time curve for single sucrose, 50 mg R-sucrose, 100 mg R-sucrose coadministration (mean ± SD, n = 12). R, reference formulation (Glucobay, produced by Bayer Pharma AG, Germany).

drug + sucrose were logarithmically transformed and compared using the geometric least-squares mean and $P < .05$. The data showed that 50 mg acarbose had hypoglycemic effects and the 50-mg dose group was used for study B.

Study B

A total of 170 subjects were screened in this trial, 60 of whom met the inclusion criteria and 54 of whom completed the study. Only 4 completed the first cycle

Table 4. After a Single Oral Administration of Drug + Sucrose or Single Sucrose in Healthy Subjects on an Empty Stomach Analyzed by Logarithmic Transformation Variance Analysis (BES)

Study	Parameters	Source of Variation	*F*	*P*
Study A	C_{max} (mg/100 mL)	Period	1.793	0.170
		Sequence	0.498	0.694
		Drug	32.259	< 0.001
	$AUC_{0\text{-}2h}$ (mg·h/100 mL)	Period	0.996	0.408
		Sequence	0.802	0.527
		Drug	24.960	< 0.001
Study B	C_{max} (mg/100 mL)	Period	3.067	0.051
		Sequence	0.339	0.887
		Drug	114.539	< 0.001
	$AUC_{0\text{-}2h}$ (mg·h/100 mL)	Period	1.722	0.184
		Sequence	0.580	0.715
		Drug	63.845	< 0.001

$AUC_{0\text{-}2h}$, area under the serum glucose-time curve obtained after deducting the zero baseline; C_{max}, maximum value of serum glucose after deducting the zero baseline.

of biological sample collection, and only the first-cycle data were included in the FAS, PDPS, and BES. One subject decided to withdraw from the study after signing the informed consent form, and the data of this subject were not included in the FAS, PDPS, and BES. One subject had decreased serum glucose concentration 100 and 120 minutes after taking sucrose in the first cycle and did not take medication in the second and third cycles. The data of this subject in the first cycle included C_{max} in PDPS and BES, and the $AUC_{0\text{-}2h}$ did not include PDPS and BES. The remaining subjects (31 men and 28 women) completed the trial, and the data were included in the FAS, PDPS, and BES. Median age was 27.5 ± 6.6 years, weight was 57.7 ± 7.4 kg, height was 162.7 ± 7.8 cm, and BMI was 21.7 ± 1.4 kg/m^2. PK parameters (PDPS) of healthy subjects after single oral administration of sucrose alone or 50 mg acarbose-sucrose is shown in Table 3. After fasting single oral of sucrose alone, 50 mg R-sucrose, and 50 mg T-sucrose, the blood sugar C_{max} was 61.4 ± 18.0, 31.7 ± 13.9, and

Table 5. Pairwise Comparison of the Pharmacodynamic Parameters in Study A and Study B

Study	Parameters	*F*	*P*	LS Means
Study A	C_{max} (mg/100 mL)	6.121	< 0.001	LS means (sucrose + 50 mg R vs sucrose)
		9.559	< 0.001	LS means (sucrose + 100 mg R vs sucrose)
	$AUC_{0\text{-}2h}$ (mg·h/100 mL)	6.367	< 0.001	LS means (sucrose + 50 mg R vs sucrose)
		8.211	< 0.001	LS means (sucrose + 100 mg R vs sucrose)
Study B	C_{max} (mg/100 mL)	13.660	< 0.001	LS means (sucrose + 50 mg T vs sucrose)
		12.459	< 0.001	LS means (sucrose + 50 mg R vs sucrose)
	$AUC_{0\text{-}2h}$ (mg·h/100 mL)	10.029	< 0.001	LS means (sucrose + 50 mg T vs sucrose)
		9.506	< 0.001	LS means (sucrose + 50 mg R vs sucrose)

$AUC_{0\text{-}2h}$, area under the serum glucose-time curve obtained after deducting the zero baseline; C_{max}, maximum value of serum glucose after deducting the zero baseline; LS mean, least-squares mean.

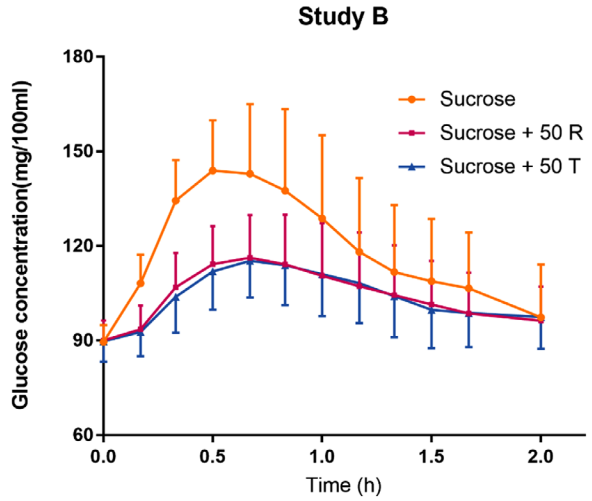

Figure 2. Mean serum glucose concentration-versus-time curve for single sucrose, 50 mg R-sucrose, 50 mg T-sucrose coadministration (mean ± SD, n = 54). R, reference formulation (Glucobay, produced by Bayer Pharma AG, Germany). T, test formulation (acarbose tablets, produced by China Resources SECCO Pharmaceuticals Co., Ltd.).

29.2 ± 12.4 mg/100 mL, respectively, and the blood sugar $AUC_{0\text{-}2h}$ was 61.6 ± 27.2, 31.8 ± 18.8, and 29.7 ± 15.2 mg·h/100 mL, respectively. Healthy subjects' average serum glucose concentration-time chart after single oral administration of sucrose alone or drug + sucrose is shown in Figure 2. Compared with the sucrose alone group, acarbose in the test or reference formulation group had statistical significance in reducing blood sugar ($P < .001$; Table 4). After logarithmic transformation of the C_{max} and $AUC_{0\text{-}2h}$ in healthy subjects taking sucrose alone or drug + sucrose in a single oral administration, the geometric least-squares mean was calculated, and the P was <.001. The test formulation (or reference formulation) had statistical difference as the sucrose alone (Table 5). The C_{max} and $AUC_{0\text{-}2h}$ of healthy subjects taking sucrose alone and drug + sucrose in a single oral dose were analyzed by logarithmic conversion using the linear mixed-effects model. The geometric mean ratios (test preparation/reference preparation) were 92.68% and 95.70%, respectively, with 90%CIs of 84.08% to 102.17% and 84.21% to 108.76%, respectively, which fell between 80.00% and 125.00% (Table 6).

Discussion

In study A and study B, subjects took sucrose alone; the serum glucose value of this cycle was used as baseline and the QC point to evaluate the hypoglycemic effects of different doses of acarbose in the human body. No statistical difference between QC serum glucose indicated that there was no difference between each cycle, allowing hypoglycemic comparison of acarbose between different cycles to be performed. In study A and study B, there was no statistical difference between the single doses of sucrose between each cycle ($P > .05$; Table 4). Only when there was a statistical difference between the serum glucose level after taking the medicine and the serum glucose level without taking the medicine could the difference in the hypoglycemic effect between different doses be evaluated. In study A and study B, our results showed that there was a statistical difference between serum glucose level after drug administration and serum glucose level without medication (Table 5). In study B, the results also showed that the 90%CI of the geometric mean of C_{max} and $AUC_{0\text{-}2h}$ was also in the range of BE (Table 6). The 3 × 3 crossover Latin design method uses the sucrose group as a separate cycle. It is not only used as a basic value to compare the hypoglycemic effect of acarbose but also used as a QC to improve the accuracy of statistics and reduce the amount of blood collected by the subjects. The corrected PD parameter evaluation method can distinguish the hypoglycemic effects of different doses of acarbose, and can also reduce the number of subjects required to meet the BE standard.

The results of our study showed that setting the blood collection time to 0–2 hours can prevent the

Table 6. Healthy Subjects Take 50-mg Acarbose Tablets and Sucrose Bioequivalence Statistics (BES)

Parameters	Geometric mean		GMR	CV (%)	90%CI (%)
	Sucrose + 50 mg T	Sucrose + 50 mg R			
C_{max} (mg/100 mL)	26.8	29.0	0.9268	31.42	84.08-102.17
$AUC_{0\text{-}2h}$ (mg·h/100 mL)	26.0	27.2	0.9570	41.85	84.21-108.76

$AUC_{0\text{-}2h}$, area under the serum glucose-time curve obtained after deducting the zero baseline; C_{max}, maximum value of serum glucose after deducting the zero baseline; CV, coefficient of variation; GMR, geometric mean ratio; CI, confidence interval.

negative value of PD parameters and at the same time can reduce the subject's blood collection and the complexity of clinical operations. In study A, we determined that the effective dose for the formal trial is 50 mg, which is different from the current data reported in domestic and foreign studies.[8–10,14] In study B, we showed that the 50-mg doses of the reference formulation and test formulation are BE.

Conclusion

The effective dose of acarbose in healthy Chinese volunteers was 50 mg. The reference formulation and test formulation were BE.

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Conflicts of Interest

The authors report no declarations of interest.

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