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Original Research

Safety, tolerability, and pharmacokinetics of aildenafil citrate tablets, a novel oral PDE5 inhibitor, in healthy Chinese volunteers after multiple-dose administration

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Abstract

Background: Aildenafil citrate is a potent and selective inhibitor of cyclic guanosine monophosphate–specific phosphodiesterase type 5, developed for the treatment of erectile dysfunction (ED).
Aim: This study aimed to assess the pharmacokinetics, safety, and tolerability of aildenafil citrate tablets after multiple doses in healthy Chinese males.
Methods: Twenty participants were divided into 2 groups, 10 participants each. Participants were administered multiple doses of aildenafil citrate tablets at 30 and 60 mg.
Outcomes: The safety evaluation was based on clinical symptoms and adverse events. Concentrations of aildenafil and its key metabolites (M1, M5, and M12) in human serum were measured by liquid chromatography–tandem mass spectrometry.
Results: Pharmacokinetic analysis showed rapid absorption and elimination of aildenafil, with a median time to maximum serum concentration of 1 hour and mean terminal half-lives of 2.75 and 3.26 hours in the respective dose groups. The mean maximum concentration was proportional to the aildenafil dose in the range of 30 to 60 mg, although the area under the curve was not proportional for serum concentration vs time 0 to the last measurable time point (24 hours). Multiple doses of aildenafil were well tolerated, with 60.0% of men experiencing treatment-emergent adverse events, notably myalgia and fatigue, particularly in the 60-mg group.
Clinical Implications: Aildenafil citrate tablets demonstrated favorable tolerability with once-daily administration over the clinical dose range. The occurrence of myalgia and fatigue was more prevalent in the 60-mg group. From a pharmacokinetic perspective, optimal administration of aildenafil citrate tablets appears to be 1 hour before sexual intercourse in men with ED.
Strengths and Limitations: This study presents robust safety and pharmacokinetic data at expected therapeutic doses, unaffected by clinical factors. The efficacy of aildenafil citrate tablets warrants further validation in individuals with ED.
Conclusion: Aildenafil citrate tablets exhibited good tolerability in healthy Chinese males following multiple doses at 30 and 60 mg. The 60-mg group showed an increased incidence of myalgia and fatigue, suggesting the need for heightened clinical vigilance. The mean maximum concentration, but not the area under the curve, displayed dose proportionality within the 30- to 60-mg dose range, and no significant drug accumulation was observed with repeated daily administration.
Clinical Trial Registration: CTR20192473 (http://www.chinadrugtrials.org.cn).

Keywords: phosphodiesterase inhibitor; pharmacokinetic; safety; multiple doses.

Introduction

Erectile dysfunction (ED) is a common male sexual dysfunction that significantly affects the quality of life for patients and their partners.[1] Treatment options for ED range from non-invasive to invasive methods: vacuum constriction therapy, penile self-injection regimens, penile prostheses, and notably phosphodiesterase type 5 (PDE5) inhibitors. Due to their ease of use, impressive efficacy, and favorable tolerability, PDE5 inhibitors are recommended as the primary line of treatment for ED.[2]

Currently, the Food and Drug Administration–approved PDE5 inhibitors are sildenafil, tadalafil, vardenafil, and avanafil. These compounds have clearance for various indications, such as ED, pulmonary artery hypertension, and lower urinary tract symptoms. Additionally, their therapeutic potential extends to a diverse array of conditions: diabetes, postprostatectomy complications, depression, stroke, heart failure, COVID-19, and other ailments.[3,4]

Aildenafil citrate, a novel Chinese development, is a potent and highly selective inhibitor of cyclic guanosine monophosphate–specific PDE5, designed for treating ED.[5] Aildenafil citrate's structure uniquely includes secondary amine and dimethyl groups. These structural characteristics provide advantages such as enhanced coplanarity, increased lipid solubility, and a more balanced lipid-water distribution ratio when compared with other PDE5 inhibitors. Conse-

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quently, these features facilitate superior absorption and distribution within the body. Notably, aildenafil citrate's inhibitory effects on PDE5 enzyme activity are 1.47 times more potent than comparable products. In relation to PDE3, PDE6, PDE9, and PDE11 enzymes, the inhibition ratios for aildenafil citrate are 0.75, 0.30, 0.06, and 0.49, respectively, relative to similar products. This profile contributes to the lower incidence of adverse drug reactions associated with aildenafil citrate.[4] In 2021, the aildenafil citrate tablet received National Medical Products Administration approval as an innovative drug.[6] The recommended dosage in the drug instruction is a 60 mg, taken approximately 1 hour before sexual activity, with a maximum frequency of once within a 24-hour period, not exceeding 12 weeks. This study serves as a supplementary phase 1 clinical trial, prompted by changes in the manufacturing process, with the aim of elucidating the safety and pharmacokinetics of aildenafil citrate tablets in healthy Chinese males following multiple-dose administration.

Methods

Study population

The eligibility criteria were healthy Chinese males aged 22 to 45 years, willing and capable of adhering to the study schedule and assessments. Participants needed to weigh at least 50 kg and have a body mass index between 19.0 and 24.0 kg/m^2. Additionally, participants had to show no signs of clinically significant abnormalities in physical examinations, medical histories, clinical laboratory assessments, vital signs, and electrocardiograms. Nonsterilized males who were committed to using effective contraception throughout the study and for 3 months after the final dose were included.

Exclusion criteria encompassed individuals with clinically significant diseases or major surgical procedures within 4 weeks before the study; recent use of prescriptions, over-the-counter medications, or nutraceutical products within the last 2 weeks prior to the trial; or current use of nitrates or nitric oxide donor drugs. Participants were also ineligible if they demonstrated known hypersensitivity to any component of the study drug formulation or PDE5 inhibitors; tested positive for chronic hepatitis B or C virus, syphilis, or HIV antibodies; had poor peripheral venous access; or had donated >400 mL of blood within the preceding 3 months. History or evidence of alcohol or drug abuse also led to exclusion.

Study design

Conducted at the phase 1 unit of Peking University First Hospital, this study was an open-label, single-center, phase 1 investigation involving healthy Chinese males. Ethical approvals were obtained from the Ethics Committee of Peking University First Hospital, with approval granted for study protocol and informed consent documents (ethical approval 2019, drug registration 67). All procedures involving human participants adhered to the ethical standards of the responsible committee on human experimentation (institutional and national) and followed the Declaration of Helsinki and good clinical practice guidelines. Prior to participation, all participants provided written informed consent. The study was registered on the China Drug Trials official website (CTR20192473; http://www.chinadrugtrials.org.cn). Twenty participants were enrolled and divided into 2 dose groups. Each group received multiple doses of aildenafil citrate tablets over a 5-day period, with doses set at 30 and 60 mg daily after an overnight fast. During their stay at the clinical trial center, participants adhered to standardized diets. The administration of aildenafil citrate tablets occurred once daily for 5 days, and participants remained under observation for 24 hours after the final administered dose. After collection of all biological samples and completion of study assessments, participants were released from the center upon investigator approval. On day 8, a clinical follow-up visit took place, including fasting, for safety assessments. These evaluations included vital signs, a 12-lead electrocardiogram, clinical laboratory tests, physical examinations, and ophthalmologic examinations.

Blood sampling

Blood samples for pharmacokinetic analysis were collected at various time points: predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours postdose on days 1 and 5, as well as predose on days 3 and 4. At each specified point, a 5-mL blood sample was drawn and subsequently centrifuged at 3500 rpm for 10 minutes at 4 °C. The resulting serum samples were stored at −70 °C until ready for analysis.

Pharmacokinetic analysis

To quantify aildenafil and its metabolites (M1, M5, and M12) in serum, a Shimazu liquid chromatography system paired with a SCIEX Triple Quad 5500 mass spectrometer was utilized. The analysis employed an isotope-labeled internal standard, and an Eclipse Plus C18 column served as the analytical column. Acetonitrile and 5mM ammonium formate in water (with 0.5% formic acid) were the mobile phases, flowing at rate of 0.7 mL/min. The column was maintained at 40 °C, and the mass spectrometer operated in a positive scan mode. Quantitation was carried out through triple-quadrupole mass spectrometry with the MRM mode (multiple-reaction monitoring). Linear calibration ranges for aildenafil and its metabolites spanned 0.5 to 1000 ng/mL, with limits of quantification set at 0.500 ng/mL. All samples underwent analysis within established storage stability periods.

Pharmacokinetic parameters were derived from serum concentration-time profiles of aildenafil and its 3 principal metabolites (M1, M5, and M12). This involved a noncompartmental analysis approach with WinNonlin Professional version 8.1 covering all eligible participants. Determined pharmacokinetic parameters were maximum concentration (C_{max}), steady-state C_{max} ($C_{max,ss}$), minimum concentration at steady state ($C_{min,ss}$), and time to reach C_{max} or $C_{max,ss}$ (T_{max}). These metrics were established by collating observed data. Additional parameters computed were area under the curve (AUC), representing serum concentration from time 0 to the final measurable time point (24 hours; $AUC_{0\text{-}24}$). Similarly, calculations were made for the AUC encompassing a dosing interval at steady state ($AUC_{0\text{-}24,SS}$), the terminal half-life ($T_{1/2}$), and accumulation ratios. Accumulation ratios were expressed as follows: $R_{acc}(AUC_{0\text{-}24}) = AUC_{0\text{-}24}$ on day 5/$AUC_{0\text{-}24}$ on day 1; $R_{acc}(C_{max}) = C_{max,ss}$ on day 5/C_{max} on day 1.

Safety analysis

Safety information for all enrolled participants was closely monitored throughout the study. Monitoring included various assessments, such as physical examinations, ophthalmologic examinations, vital signs, electrocardiograms, and laboratory

Table 1. Participants' demographic and baseline characteristics.

	Aildenafil citrate	
	30 mg	**60 mg**
Age, y		
Mean ± SD	31.4 ± 6.17	32.1 ± 5.04
Range	22-43	23-42
Median	31.5	32.5
Height, cm		
Mean ± SD	170.9 ± 4.36	168.9 ± 5.00
Range	162-179	162-176
Median	172.0	169.5
Weight, kg		
Mean ± SD	64.65 ± 7.082	60.06 ± 4.461
Range	54.6-76.1	52-66
Median	64.90	61.25
Body mass index, kg/m^2		
Mean ± SD	22.11 ± 1.793	21.07 ± 1.441
Range	19.1-24	19.3-23.8
Median	22.50	20.80

tests (hematology, blood chemistry, blood coagulation function, and urinalysis). Adverse events (AEs) occurring from the initial administration of the study drug until study completion were evaluated by the investigator for their severity (mild, moderate, or severe) and their relationship to the study drug.

Statistical methods

Pharmacokinetic parameters were derived with the noncompartmental model within Phoenix WinNonlin version 8.1. All additional statistical analyses were performed with SAS version 9.4. The evaluation of dose proportionality across various doses for C_{max} and AUC values employed the power model.[7,8] The analytical cohorts, including the safety analysis set and the pharmacokinetic set, comprised all duly enrolled participants who received at least 1 dose of the investigational drug. For inclusion in the pharmacokinetic set, the presence of at least 1 measurable blood concentration of the drug was also required.

Tabulations presenting the count and proportion of participants experiencing treatment-emergent AEs were outlined according to the organ class and preferred terms of the MedDRA system (Medical Dictionary for Regulatory Activities), categorized by severity and their relationship to the study drug. Coding of treatment-emergent AEs was based on MedDRA version 20.0.

Results

Demographic and baseline characteristics

Ninety-two volunteers underwent screening for study participation, and 20 were enrolled, with each dose group consisting of 10 volunteers. Unfortunately, 1 participant withdrew due to an AE, specifically vomiting on day 5. All participants providing assessable data were included in the safety analysis set. For pharmacokinetic analysis, data from 20 men were utilized, excluding 1 participant who discontinued the study on day 5, with parameters influenced by the withdrawal omitted from certain parameter calculations. Demographic and baseline characteristics demonstrated comparability across all dose groups. Detailed demographic attributes of the participants are presented in Table 1.

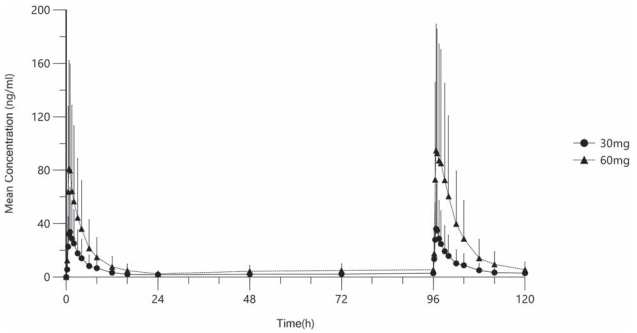

Figure 1. Mean aildenafil serum concentrations following multiple once-daily dosing (days 1 and 5).

Pharmacokinetic assessments

The pharmacokinetic analysis involved all 20 men, and the mean serum concentration-time curve for the initial dose segment is illustrated in Figure 1. Examination of the pharmacokinetics revealed the swift absorption of aildenafil, with a median time to C_{max} (T_{max}) of 1 hour (range, 0.50-2.00 hours) for the initial doses of 30 and 60 mg. The elimination of aildenafil occurred relatively promptly, with a geometric mean $T_{1/2}$ of 2.75 and 3.26 hours within each dose group. The geometric mean C_{max} and AUC from time 0 to 24 hours ($AUC_{0\text{-}24}$) were 81.03 and 199.10 ng/mL and 313.78 and 963.18 h·ng/mL, respectively. Based on the power model evaluation, the 95% CI for the parameter β yielded values of 0.755 to 1.839 for C_{max} and 1.035 to 2.201 for $AUC_{0\text{-}24}$, confirming dose proportionality for C_{max} (but not $AUC_{0\text{-}24}$) across doses ranging from 30 to 60 mg.

Aildenafil undergoes metabolism primarily via CYP3A4 and CYP2C9, resulting in several metabolites. Foremost among these are metabolites M1, M5, and M12 in the serum. Similar to aildenafil, the metabolites M1, M5, and M12 achieved peak serum concentrations between 0.63 to 1.00 hour. Their respective geometric mean half-lives were observed at 8.33 to 9.16 hours, 5.61 to 7.77 hours, and 1.70 to 3.34 hours across groups. Notably, the $AUC_{0\text{-}24}$ for M1 was approximately 2-fold greater than M5 and 10-fold greater than M12. The hierarchy of C_{max} values for these metabolites can be ranked as follows: M1 > M5 > M12.

For the steady-state phase, the serum concentration-time profiles are illustrated in Figure 1. No significant alterations in T_{max} were observed on day 5 vs day 1. The R_{acc} values were 1.04 and 1.61 for C_{max} and 1.05 and 1.75 for $AUC_{0\text{-}24}$, respectively, indicating negligible drug accumulation upon daily multiple dosing of 30 or 60 mg. A parallel pattern was evident among the primary metabolites. The principal pharmacokinetic parameters of aildenafil and its 3 key metabolites on days 1 and 5 are concisely summarized in Table 2.

Safety outcomes

The safety evaluation included comprehensive data from all 20 participants who received multiple administrations of aildenafil citrate tablets. A concise overview of AEs documented during the study is meticulously presented in Table 3. One participant chose to discontinue his participation due to an AE, specifically vomiting on day 5. In total, 26 instances of AEs spanning 12 participants were assessed by the investigator to be linked to the study drug. Among the observed AEs, myalgia, fatigue, nasal congestion, and flushing

Table 2. Pharmacokinetic parameters of aildenafil citrate following oral administration of multiple doses: 30 or 60 mg once daily.[a]

	30 mg ($n = 10$)		60 mg ($n = 10$)	
Parameter	**Day 1**	**Day 5**	**Day 1**	**Day 5**
Aildenafil				
C_{max} or $C_{max,ss}$, ng/mL	81.03 (45.3)	84.61 (55.9)	199.10 (37.8)	319.71 (23.8)
$C_{min,ss}$, ng/mL		1.05 (75.7)[b]		3.61 (61.3)
T_{max}, h	1.00 (0.50-2.00)	0.75 (0.25-2.00)	1.00 (0.50-2.00)	0.88 (0.50-3.00)
AUC_{0-24}, h·ng/mL	313.78 (45.3)	346.23 (51.8)[b]	963.18 (44.8)	1683.67 (45.1)
$T_{1/2}$, h	2.75 (21.2)	3.61 (38.1)[b]	3.26 (19.7)	3.38 (24.2)
C_{24}, ng/mL	0.35 (146.6)	0.92 (148.0)[b]	1.71 (54.1)	3.85 (66.8)
R_{acc}				
C_{max}		1.04 (50.6)		1.61 (24.2)
AUC_{0-24}		1.05 (28.8)[b]		1.75 (23.3)
M1				
C_{max} or $C_{max,ss}$, ng/mL	31.26 (43.9)	35.82 (41.3)	68.51 (48.0)	51.16 (43.4)
$C_{min,ss}$, ng/mL		4.23 (111.7)[b]		8.48 (39.6)
T_{max}, h	1.00 (0.75-2.00)	1.00 (0.50-2.00)	0.75 (0.50-1.00)	1.00 (0.75-1.50)
AUC_{0-24}, h·ng/mL	151.42 (78.4)	228.09 (85.7)[b]	290.61 (48.9)	462.44 (31.4)
$T_{1/2}$, h	8.33 (64.4)	11.32 (44.3)[b]	9.16 (27.1)	14.36 (23.2)
C_{24}, ng/mL	2.32(77.6)	5.49(75.7)	3.96(62.0)	10.09(32.7)
R_{acc}				
C_{max}		1.15 (23.4)		0.75 (43.2)
AUC_{0-24}		1.42 (23.2)[b]		1.59 (30.3)
M5				
C_{max} or $C_{max,ss}$, ng/mL	19.34 (31.5)	17.44 (32.2)	43.44 (31.2)	34.93 (27.4)
$C_{min,ss}$, ng/mL		0.76 (26.6)[b]		1.91 (26.1)
T_{max}, h	0.75 (0.50-1.50)	0.75 (0.50-1.00)	0.63 (0.50-0.75)	0.75 (0.50-2.00)
AUC_{0-24}, h·ng/mL	64.50 (18.8)	68.71 (20.4)[b]	147.96 (17.2)	178.59 (16.6)
$T_{1/2}$, h	5.61 (49.2)	7.84 (28.3)[b]	7.77 (13.9)	8.73 (18.7)
C_{24}, ng/mL	0.24(130.6)	0.69(49.8)	1.14(24.7)	2.08(23.3)
R_{acc}				
C_{max}		0.90 (36.4)		0.80 (43.3)
AUC_{0-24}		1.03 (10.5)[b]		1.21 (9.4)
M12				
C_{max} or $C_{max,ss}$, ng/mL	6.99 (37.5)	6.84 (37.8)	15.34 (36.4)	13.26 (40.9)
$C_{min,ss}$, ng/mL		NA		NA
T_{max}, h	0.75 (0.50-1.50)	0.75 (0.50-1.00)	0.63 (0.50-0.75)	0.75 (0.50-1.50)
AUC_{0-24}, h·ng/mL	14.61 (33.0)	14.61 (41.8)[b]	36.22 (23.7)	45.25 (31.1)
$T_{1/2}$, h	1.70 (33.9)	2.02 (37.5)[b]	3.34 (38.8)	3.83 (23.1)
C_{24}, ng/mL	0	0	0	0
R_{acc}				
C_{max}		0.98 (35.3)		0.86 (45.6)
AUC_{0-24}		1.02 (9.5)[b]		1.25 (12.3)

Abbreviations: AUC_{0-24}, area under the curve from time 0 to the final measurable time point (24 hours); C_{24}, concentration at 24 hours; C_{max}, maximum concentration; $C_{max,ss}$, steady-state C_{max}; $C_{min,ss}$, minimum concentration at steady state; NA, not applicable; R_{acc}, accumulation ratio; $T_{1/2}$, terminal half-life; T_{max}, time to reach C_{max} or $C_{max,ss}$. [a]All data are presented as geometric mean (CV%; ie, pseudo within-subject percentage coefficient of variance) except T_{max}, which is presented as median (range), and C_{24}, which is presented as mean (SD). [b]Sample size is 9.

were recurrently reported. These occurrences were captured through investigator observation, physical examinations, or participant reports. The occurrences of myalgia and fatigue displayed a discernible increment in a manner that correlates with the administered dose, particularly confined to the 60-mg group. These instances manifested from day 2 or 3 and persisted for several days. In contrast, other AEs did not demonstrate a dose-dependent trend. Regarding the laboratory assessment facet, only 2 men within the 60-mg group encountered 3 instances of AEs. In 1 instance, a participant exhibited a decline in lymphocyte count and percentage from 1.70×10^9/L (33.9%) during the screening to 0.80×10^9/L (12.9%) on day 4, eventually rebounding after 2 days on day 6. In another case, an elevation in blood glucose was observed from 4.22 mmol/L during the screening to 6.21 mmol/L on day 6, subsequently normalizing after 2 days on day 8. Notably, no other conspicuous anomalies were ascertained in vital signs or electrocardiogram recordings over the duration of the trial.

Discussion

The mechanism of action of aildenafil citrate mirrors that of sildenafil, enhancing certain responses to nitric oxide by inhibiting downstream cyclic guanosine monophosphate degradation. This investigation meticulously assessed the safety, tolerability, and pharmacokinetics of aildenafil citrate in a cohort of healthy Chinese males. The administered 5-day multiple once-daily doses at 30- and 60-mg levels were well tolerated, causing no clinically significant impact on heart rate, blood pressure, or visual function. Notably, no fatalities or serious AEs were recorded, and all observed

Table 3. Summary of adverse events.

	30 mg		60 mg	
	Participants, No. (%)	Cases, No.	Participants, No. (%)	Cases, No.
Adverse events	4 (40.0)	9	10 (100.0)	20
Infectious and infective diseases				
Upper respiratory infection	0 (0)	0	2 (20.0)	2
Musculoskeletal and connective tissue diseases				
Myalgia	0 (0)	0	5 (50.0)[a]	6[a]
Fatigue	0 (0)	0	2 (20.0)[a]	2[a]
Respiratory, chest, and mediastinal diseases				
Nasal congestion	2 (20.0)[a]	3[a]	2 (20.0)[a]	3[a]
Ocular organ disease				
Ocular paresthesia	0 (0)	0	1 (10.0)[a]	1[a]
Vascular and lymphatic diseases				
Flushing	3 (30.0)[a]	4[a]	0 (0)	0
Systemic disease and various reactions at the site of administration				
Pyrexia	0 (0)	0	1 (10.0)[a]	1[a]
Chest discomfort	1 (10.0)[a]	1[a]	0 (0)	0
Influenza-like illness			1 (10.0)	1
All kinds of neurologic diseases				
Head discomfort	0 (0)	0	1 (10.0)[a]	1[a]
Gastrointestinal diseases				
Vomiting	1 (10.0)[a]	1[a]	0 (0)	0
Laboratory evaluations				
Lymphocyte count: decreased	0 (0)	0	1 (10.0)[a]	1[a]
Lymphocyte percentage: decreased	0 (0)	0	1 (10.0)[a]	1[a]
Blood glucose: elevated	0 (0)	0	1 (10.0)[a]	1[a]

[a] Adverse events that were considered probably or possibly related to the study drug.

AEs exhibited mild to moderate severity. Prominent AEs included myalgia, fatigue, nasal congestion, and flushing, aligning with the profiles of other PDE5 inhibitors.[1,2,9] These events are often attributed to the nonselective inhibition of additional PDE isoenzymes within the body.[2,4] Instances of myalgia and fatigue exhibited a dose-dependent increase exclusively within the 60-mg group. Efforts to elucidate the potential causative factors for myalgia and fatigue included creatine kinase assessments on day 4, which failed to reveal any noteworthy deviations when compared with baseline, indicating no association with muscular injury. Comparative analysis revealed that tadalafil, similar to aildenafil, elicits a higher frequency of myalgia and back pain that typically take hours to alleviate. This observation underscores the relevance of phosphodiesterase isoenzymes in different tissues, suggesting that variations in selectivity toward these isoenzymes could account for the differential side effect profile, particularly myalgia, with tadalafil as compared with other PDE5 inhibitors.[4] Consequently, our findings suggest that such AEs may manifest in clinical practice, particularly at higher dosage levels. One participant in the 60-mg group exhibited a transient grade 1 decrease in lymphocyte count. Several plausible explanations for this AE are postulated. First, an increase in the proportion of monocytes in 2 participants within the same group was noted, attributed to upper respiratory tract infection and influenza, both involving immune responses to bacterial and viral invaders. Second, an examination of safety data for analogous products containing aildenafil citrate revealed instances of white blood cell–related AEs, though the direct correlation with sildenafil remains uncertain. Despite similarities with sildenafil, the mild decrease in lymphocyte count associated with aildenafil did not induce significant harm to the men. Continued vigilance regarding the occurrence of such AEs remains paramount in future investigations.

The main goal of this study was to examine how the body processes aildenafil after administration of several daily doses to healthy Chinese males. Aildenafil was quickly absorbed, reaching its highest concentration 1 hour after either the 30- or 60-mg initial dose. After the first dose, the amount of aildenafil in the blood was less than 1/20th of the C_{max} observed at 24 hours later. The average time that it takes for the body to eliminate half of the aildenafil ($T_{1/2}$) ranged from 2.75 to 3.26 hours. During the steady-state phase, there was no significant buildup of the drug when the 30- or 60-mg doses were given once daily. The pharmacokinetic features—such as easy administration, rapid absorption, appropriate half-life, and no buildup with repeated once-daily use—are favorable for an ideal oral agent that treats ED. Importantly, aildenafil's pharmacokinetic profile is similar to that of sildenafil and vardenafil.[10,11] An analysis of exposure with a power model showed that C_{max}, but not the AUC, had a proportional increase with the dose across the 2 given doses. On the first day, the AUC exhibited more than a proportional increase between the 30- and 60-mg initial doses. Notably, on the fifth day, the AUC for the 60-mg group significantly increased as compared with the first day. This substantial increase could be linked to the occurrence of dose-related AEs, such as myalgia and fatigue.

A preliminary previously unreported in vitro study indicated the involvement of CYP3A4 and CYP2C9 in the metabolism of aildenafil, resulting in the creation of 3 main metabolites—M1, M5, and M12—with M1 being the primary metabolite. As the administered dose increased, key pharmacokinetic parameters, including C_{max} and AUC, demonstrated a consistent upward trend for the 3 metabolites.

Interestingly, the $T_{1/2}$ of M1 and M5 was notably prolonged, while M12 exhibited no significant change. Crucially, there was no observable accumulation for the 3 main metabolites in the 2 dose groups.

Conclusion

The results of this investigation highlight the favorable tolerability profile of aildenafil in healthy Chinese males receiving multiple daily doses of 30 and 60 mg. Notably, the potential for an increased occurrence of myalgia and fatigue requires careful consideration, especially in the 60-mg group. Dose proportionality was established for C_{max}, but not $AUC_{0\text{-}24}$, across the administered doses ranging from 30 to 60 mg, confirming the consistent pharmacokinetic behavior of the drug. Importantly, the assessment of multiple daily administrations revealed no significant drug accumulation of the drug.

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Author contributions

Conception and design: Y.C., X.Z., R.X. Acquisition of data: R.X., B.J., L.C., N.Z., X.H. Analysis and interpretation of data: R.X., B.J., L.C., N.Z., X.H., X.W., X.Z., Y.C. Drafting the article: R.X. Revising it for intellectual content: R.X., B.J., L.C., N.Z., X.H., X.W., X.Z., Y.C. Final approval of the completed article: R.X., B.J., L.C., N.Z., X.H., X.W., X.Z., Y.C.

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Conflict of interest

X.W. is an employee of Youcare Pharmaceutical Group Co, Ltd, which sponsored the clinical trial. All other authors have no relevant conflicts of interest.

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