International Journal of Sciences

Research Article Volume 11 – June 2022 (06)

Population Pharmacokinetics of Naoqingzhiming Tablets a Novel Drug for Vascular Dementia in Healthy Chinese Subjects

Xin Liu[1], Pingping Lin[2], Ting Li[2], Ping Shi[2], Chenjing Wang[2], Mingxia Chen[3], Haiyan Jiang[3], Fanli Yan[3], Yahui Han[3], Lujin Li[4], Yu Cao[2]

[1]School of Pharmacy, Qingdao University, Qingdao, Shandong, China
[2]Clinical Trials Center, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China
[3]Beijing Scrianen Pharmaceutical Co., Ltd., Beijing, China
[4]Center for Drug Clinical Research, Shanghai University of Traditional Chinese Medicine, Shanghai, China

Abstract: Objective The aims of this study was to develop a population pharmacokinetic model to characterize the pharmacokinetics of Naoqingzhiming tablets (ingredient: echinacoside) following single and multiple doses in healthy Chinese subjects, and to identify covariates that might explain variability in exposure following oral administration. **Methods** Model development was achieved using data from a single- and multiple-dose studies. 1497 blood concentrations were available for population pharmacokinetics model. Population pharmacokinetic modelling was conducted using nonlinear mixed-effects modelling (NONMEM) software to estimate population pharmacokinetic parameters. **Results** A two-compartment model with first order absorption and elimination was found to best describe the pharmacokinetics of Naoqingzhiming tablets. The final model included aspartate aminotransferase (AST) as a covariate on apparent volume of distribution (V/F). The final pharmacokinetic parameter estimates were apparent clearance, 2510L/h; apparent volume of distribution, 11200L; and lag time, 0.141h. **Conclusion** The population pharmacokinetic model for Naoqingzhiming tablets identified the relationship between pharmacokinetic parameters and covariates, apparent volume of distribution was related to aspartate aminotransferase.

Keywords: Echinacoside, Population Pharmacokinetics, Modeling, Naoqingzhiming Tablets

Introduction

Dementia has become a major health problem worldwide due to the increasing aging of the population [1]. This has brought considerable economic pressure to society [2]. The most common type of dementia is Alzheimer's disease and Vascular dementia. Vascular dementia is the second most common form of dementia. Cerebrovascular events increase the risk of vascular dementia [3]. The pathogenesis of vascular dementia is unclear. Studies have shown that in many cases, the pathogenesis may be related to the interaction between cerebrovascular disease and primary neurodegenerative disease [4]. Currently, there are limited drugs available to treat VaD [5]. The clinical treatment mainly focuses on the prevention of cerebrovascular disease and the improvement of cognitive function [6]. In recent years, no new drugs for the treatment of vascular dementia have been on the market.

The composition of Naoqingzhiming Tablets in this study is echinacoside, which is extracted from Cistanche cistanche. One tablet of Naoqingzhiming Tablet (500mg) contains 180mg echinacoside. Cistanches Herba (Roucongrong in Chinese) has been used for centuries in TCM as a yang-tonic herb [7]. It is recorded in ancient Chinese herbal history that cistanche has the functions of nourishing the kidney and benefiting the marrow, filling the brain, including intelligence, enhancing memory and preventing dementia.

Echinacoside has been proven to improve learning and memory and neuroprotection in animal studies. Echinacoside has an important protective effect on the oxidative damage of nerve cells. It can also treat diseases caused by nerve ischemia [8]. Studies have shown that echinacoside can reverse the damage of dopaminergic neurons by increasing the concentration of dopamine [9]. At the same time, echinacoside protects striatal dopamine neurons by inhibiting the increase of 5-hydroxytryptamine (5-HT), dopamine, and norepinephrine caused by middle cerebral artery occlusion. It can treat brain diseases caused by ischemia [10].

Animal studies have shown that echinacoside has the effects of protecting nerve cells, improving learning and memory, anti-dementia, and has good safety. Therefore, echinacoside was developed as a drug for

Published at: http://www.ijsciences.com/pub/issue/2022-06/
DOI: 10.18483/ijSci.2594; Online ISSN: 2305-3925; Print ISSN: 2410-4477

Yu Cao, Lujin Li (Correspondence)
+86 532 82911767; Fax: +86 532 82911767

the treatment of vascular dementia, Naoqingzhiming tablets. The pharmacokinetic model of Naoqingzhiming tablets is necessary and has not previously been reported. In this study, a population pharmacokinetic analysis was performed to develop a pharmacokinetic model of Naoqingzhiming tablets using blood concentration data obtained from Phase I studies. The nonlinear mixed effect model was used to model the population PK model. In addition to the estimation of fixed effects, random effects can be quantified as variability within and between subjects. This is very valuable in the drug development process. The purpose of this study was to determine and estimate the characteristic parameters of the population PK model and effects of potential covariates of Naoqingzhiming tablets in healthy Chinese subjects.

Methods

Study Population

This study was designed as a randomized, double-blind, placebo-controlled, dose escalation clinical trial. The trial was conducted in The Affiliated Hospital of Qingdao University after being approved by medical ethics committee of Affiliated Hospital of Qingdao University (ClinicalTrials.gov; registration number: NCT0490250034). Study procedures were conducted in accordance with the Declaration of Helsinki and the principles of the International Conference on Harmonization Guidelines for Good Clinical Practice. All eligible individuals were informed about the purpose of the trial, study procedures and their risks. Written informed consent was obtained from all subjects participating in the trial.

Eligible volunteers were healthy male and female Chinese aged 18–65 years with body mass index of 19-26 kg/m^2, and a total body weight of male and female subjects was no less than 50 and 45 kg, respectively. Other eligibility criteria included no history of cardiac, hepatic, renal, gastrointestinal, or neurologic diseases. Exclusion criteria included smoking more than five cigarettes per day within the past 3 months; any clinically significant laboratory test or 12-lead ECG abnormality; history of drug abuse and/or alcoholism; intake of any other drugs, vitamins, or herbal medicine within 14 days or intake of any drugs known to influence the activity of drug metabolizing enzymes within 30 days before the first dose of the trial medication. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) and/or total bilirubin (TBIL) ≥ 1.5 times the upper limit of normal; blood creatinine (Cr), urea nitrogen (BUN) ≥ upper limit of normal, or Creatinine clearance rate <80 ml/min (creatinine clearance rate = (140-age) × body weight (Kg) / (0.818 × creatinine value), or female need to be multiplied by 0.85.

Study Design and sample analysis

Forty-two subjects received single dose escalation of Naoqingzhiming tablets that 180, 360, 720, 1080, 1620, 2160mg. Two subjects received 180 mg. For the remaining dose groups of 10 subjects, 8 received the experimental drug and 2 received a placebo. Intensive pharmacokinetic sampling was performed for each subject, with blood samples collected at 17 time points.

Twenty-four received multiple dose escalation of Naoqingzhiming tablets that 360 and 720mg. 10 subjects in each dose group received the experimental drug and two received a placebo. All subjects were taken drugs three times a day for 14 consecutive days. Intensive blood sampling on the first and fourteenth days. A total of 40 time points blood samples were collected.

Plasma concentrations of were echinacoside determined using a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method.

Base Model

Plasma concentration time data for echinacoside were modelled using a nonlinear mixed-effects approach with NONMEM (version 7.4, ICON Development Solutions, USA). All parameters were estimated using the First-Order Conditional Estimation method (FOCE) with eta-epsilon Interaction. The data were fit without introducing any covariates. The objective function value (OFV), data fitness, and parameter rationality were comprehensively compared to choose the best base model.

Random effect model

The random effects of population pharmacokinetics included inter-individual variability and residual error. An exponential model was used for inter-individual variability. The residual error model was used additive-proportional model.

Covariate Model

After the identification of the base model, scatter plots of individual PK parameters versus available demographic and biological characteristics were generated. In addition, stepwise covariate modelling (SCM) by PsN was used to initially screen for potential, significant covariates. The tested covariate models included additive, proportional and power models. All covariates were investigated by forward inclusion and backward elimination in NONMEM. Each selected covariate was first tested by a univariate NONMEM analysis to confirm its relevance.

Model Evaluation

The models predictive performance was verified by internal validation, which was based on goodness-of-fit (GOF) plots below. The accuracy and robustness of the final model were evaluated using the resampling techniques of the bootstrap method and prediction-corrected visual predictive check (VPC). The bootstrap method involves repeated random sampling of subjects in the database. Visual predictive check (VPC) is a valuable method for checking model performance.

Results

Subject Characteristics

Sixty-one subjects who received the experimental drug were included this study. The demographic and biological characteristics of the 61 healthy subjects are summarized in Table 1. In single dose escalation, one subject withdrew after taking the medication without blood sampling. A total of 14 people received placebo and were not included in the population pharmacokinetic analysis.

Group	Single dose escalation						Multiple dose escalation	
	180mg group N=2	360mg group N=8	720mg group N=8	1080mg group N=7	1620mg group N=8	2160mg group N=8	360mg group N=10	720mg group N=10
Age (year)	27.00±9.90 (20-34)	24.50±5.83 (20-34)	26.25±5.82 (18-35)	25.38±4.75 (21-31)	28.38±6.99 (22-44)	31.63±6.09 (25-40)	33.20±6.48 (24-44)	27.00±5.91 (19-35)
Gender (male/female)	2/0	4/4	6/2	7/0	4/4	5/3	7/3	8/2
Height (cm)	177.25±6.01 (173.00-181.50)	168.31±6.41 (160.50-181.00)	171.88±8.31 (161.50-182.50)	170.94±6.25 (161.00-182.00)	170.38±7.20 (162.00-184.00)	169.75±8.63 (157.50-182.00)	171.35±6.21 (160.00-179.00)	170.80±5.42 (163.00-177.00)
Weight (kg)	74.50±7.78 (69.00-80.00)	62.38±3.64 (57.50-68.00)	66.19±13.38 (50.00-85.00)	63.31±6.73 (51.00-72.00)	64.13±5.09 (56.00-69.00)	65.63±7.01 (55.00-74.50)	66.05±6.25 (55.50-77.50)	65.00±8.23 (55.00-78.50)
BMI (kg/m^2)	23.70±0.85 (23.10-24.30)	22.05±1.50 (19.70-23.80)	22.19±2.49 (19.20-25.90)	21.66±1.88 (19.30-24.50)	22.14±2.04 (19.30-25.00)	22.76±1.49 (20.50-24.60)	22.49±1.71 (20.50-25.80)	22.24±2.31 (19.90-26.00)
ALT (U/L)	19.85±3.04 (17.70-22.00)	12.95±2.50 (8.80-16.70)	14.60±4.78 (8.40-22.30)	19.49±10.37 (7.40-33.70)	18.93±14.59 (7.10-45.80)	13.66±4.56 (8.10-21.40)	14.84±4.48 (7.20-22.40)	15.87±6.33 (7.50-27.30)
AST(U/L)	16.95±0.78 (16.40-17.50)	17.64±2.74 (14.20-20.80)	16.39±2.10 (13.80-20.00)	14.87±5.06 (9.90-23.80)	17.25±5.33 (11.30-25.40)	16.55±2.36 (12.00-20.70)	15.04±3.17 (9.90-19.20)	14.82±3.78 (7.30-20.00)
TBIL (μmol/L)	14.30±0.00 (14.30-14.30)	15.60±6.62 (9.40-29.00)	15.73±7.54 (8.70-32.20)	20.40±3.63 (15.90-25.70)	15.25±5.78 (8.50-22.90)	14.91±4.36 (10.80-24.00)	12.13±3.94 (7.60-19.30)	17.10±5.66 (10.00-29.00)
Cr (μmol/L)	101.50±0.85 (100.90-102.10)	85.29±8.23 (70.30-94.50)	86.36±11.65 (69.10-99.20)	92.49±9.23 (76.70-102.40)	78.85±11.38 (67.10-97.60)	87.19±10.81 (71.50-97.80)	88.88±10.28 (76.10-107.20)	93.06±11.46 (75.60-113.00)

Figures in parentheses indicate ranges. BMI = Body mass index; TBIL = total bilirubin; ALT = alanine aminotransferase; AST = aspartate aminotransferase;
Table1 Demographic and biological characteristics of subjects included in population analysis

Basic model

All echinacoside blood concentrations were detected using a proven method with UPLC-MS/MS; 1497 blood concentrations were available for population pharmacokinetics model. The structural model was a one-compartment model with first-order absorption, and a lag time was fitted to the data. The residual variability and OFV of the one-compartment model were lower than those of the two-compartment model. The exponential model was chosen as the inter-individual variability model.

The fits for the observed value versus the PRED and the observed value versus the IPRED concentrations were judged to be good and the trend line was close to the line of unity, as shown in Figure 1A and 1B. The conditional weighted residuals (CWRES) value versus the PRED plots showed the points to be symmetrically distributed around a straight line through 0, as shown in Figure 1C. The distribution of the CWRES fits to a nearly symmetrically distribution, as shown in Figure 1D. Therefore, there was no evidence of bias. Overall, the plots indicated that the study data were sufficiently well described by the final model that was developed in this study. The basic model pharmacokinetic parameter estimates are given in Table 2.

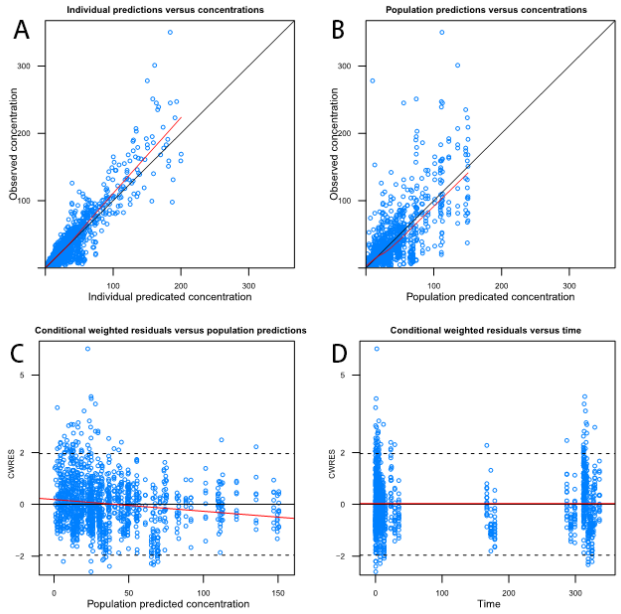

Figure1 Goodness-of-fit plots of the basic pharmacokinetic model. (A) Individual predicted concentration vs. observed concentration. (B) Population predicted concentration vs. observed concentration. The solid line in (A) and (B) is the accuracy (diagonal), and the dashed line is the fitting line. (C) Weighted residuals vs population predicted concentration. (D) Sample time vs. weighted residuals. The solid red line is the trend line

	Estimates (SE%)
Parameter	
KA, 1/h	2.67 (19.5)
CL/F, L/h	2510 (4.9)
V/F, L	11500 (5.7)
ALAG, h	0.14 (5.8)
Inter-individual variability	
CL/F, %	0.12 (16.6)
V/F, %	0.39 (22)
Residual variability	
Proportional error, %	0.41 (10.8)
Additive error, μg/L	1.01 (51.7)

Table2 Parameter estimates of the basic model

Covariate model

Eight covariates, including demographic factors and laboratory indicators, were analyzed in the present study. V/F is significantly related to AST and ALT. The effects on the OFV were investigated after each covariate was added into the pharmacokinetic basic model. The processes of stepwise establishment of the regression model and forward introduction are shown in Table 3. In the process of forward introduction, the value of the objective function decreased more than 6.63 (P<0.01), and the AST covariate decreased more significantly than ALT. Therefore, AST covariates remain in the model.

No.	Model description	OFV	-2LL
1	Basic model	8086.415	
2	Add ALT on CL/F	8078.886	-7.529
3	Add AST on CL/F	8078.595	-7.820

Table 3 Population pharmacokinetic modeling process.

Final model

The final model for Naoqingzhiming tablets population pharmacokinetics was as follows:

$$V/F = 11200 \times (AST/16.2)^{-0.639}$$

The population pharmacokinetic parameters and the estimate of parameter variance in the final model are shown in Table 4. The standard error of all the parameters was less than 30%. Figure 2 demonstrated that the observed value versus the PRED tends to have good fitness. The CWRES value versus the PRED plots showed that the points were evenly distributed around a straight line.

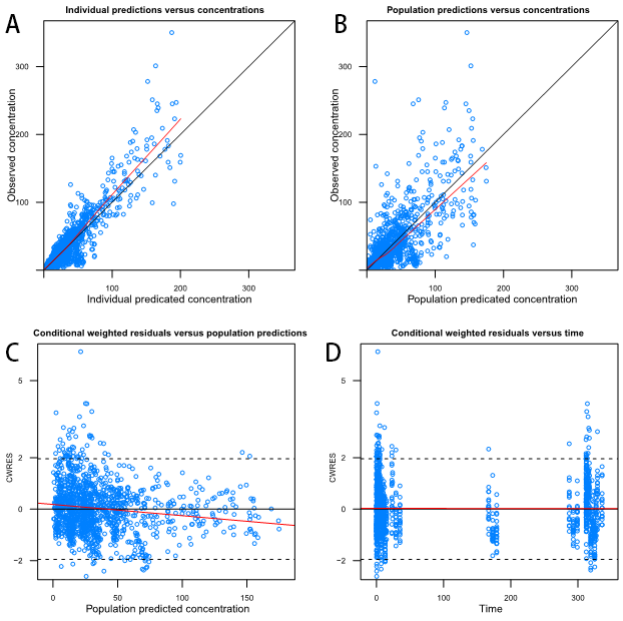

Figure2 Goodness-of-fit plots of the final pharmacokinetic model. (A) Individual predicted concentration vs. Observed concentration. (B) Population predicted concentration vs. observed concentration. The solid line in (A) and (B) is the accuracy (diagonal), and the dashed line is the fitting line. (C) Weighted residuals vs population predicted concentration. (D) Sample time vs. weighted residuals. The solid red line is the trend line

Model Validation

Model validation is very important in population analyses [11]. Bootstrap and VPC were used to evaluate model stability in the study. The results of the bootstrap method are shown in Table 4. The distribution of the simulated concentrations and observed concentrations versus time are shown in Figure 3.

Parameter	Estimates (SE%)	Bootstrap Median (2.5th, 97.5th Percentiles)
Pharmacokinetic parameter		
KA 1/h	2.67 (20.4)	2.74 (1.95~3.99)
CL/F, L/h	2510 (4.7)	2508.4 (2290.4~2774.7)
V/F, L	11200 (5.4)	11249.9 (10087.9~12541.3)
ALAG, h	0.141 (5.1)	0.140 (0.125~0.154)
θ AST on V/F	-0.639 (18.5)	-0.623 (-1.025~-0.220)
Inter-individual variability		
CL/F, %	0.339 (16.8)	0.335 (0.282~0.389)
V/F, %	0.369 (21.4)	0.360 (0.282~0.446)
Residual variability		
Proportional error, %	0.41 (10.8)	0.41 (0.37~0.45)
Additive error, μg/L	0.97 (33.9)	1.02 (0.40~1.78)

Table4 Parameter estimates of final model and bootstrap validation

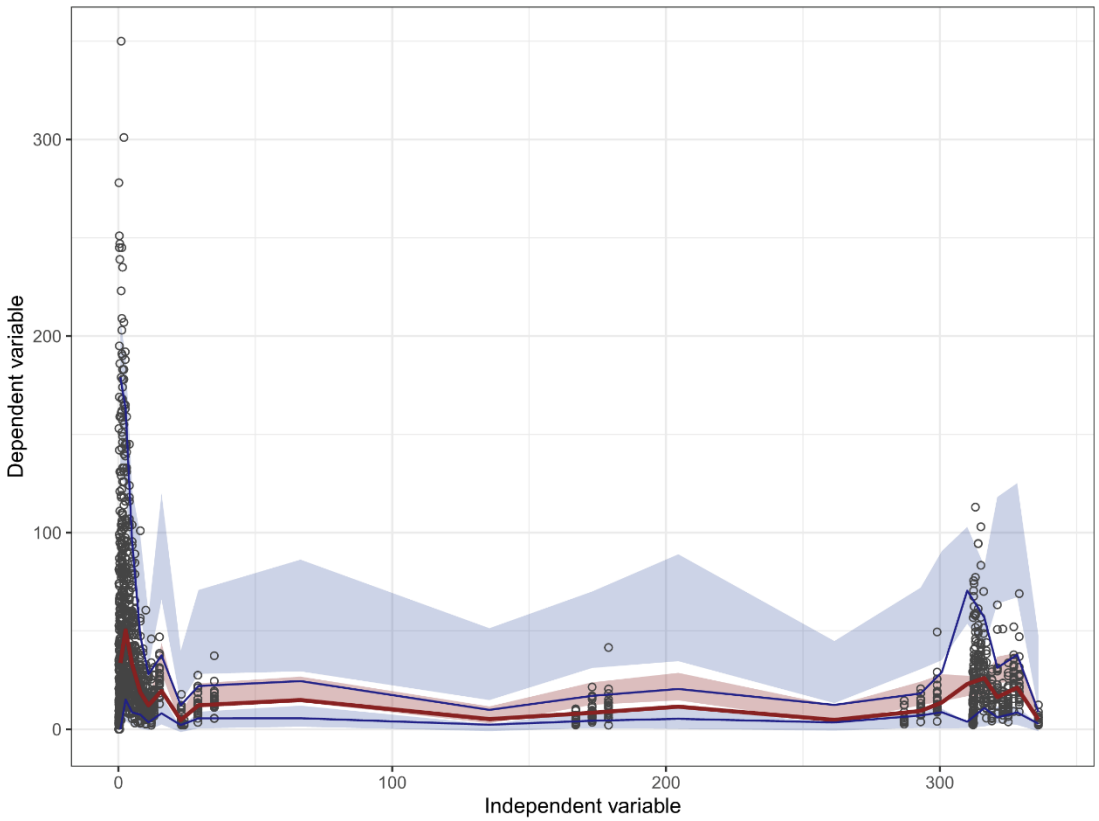

Figure3 VPC results of the final pharmacokinetic model. The circles represent the observed data. The upper and bottom shaded areas correspond to the 95% CI of the 2.5th and 97.5th percentiles and the middle shaded areas correspond to the 95% CI of the median.

Discussion

Vascular dementia is the second most common type of dementia [12], accounting for 30% in Asia and developing countries [13,14]. In clinical practice, empirical medication is usually used for VaD patients, and the medication is continued when the symptoms improve.[15]. Memantine and acetylcholinesterase inhibitors have a certain effect on VaD [5]. Cistanche deserticola is one of the most widely used "kidney Yang" tonic herbs in Traditional Chinese medicine. Echinacoside is extracted and prepared from Cistanche deserticola, which has neuroprotective effects [16]. Modern studies shown that injury and dysfunction of the hypothalamus-pituitary-target gland axis (including adrenal gland, thyroid, and gonadal glands) are the main pathological mechanisms of "Kidney Yang Deficiency Syndrome" [17]. The hypothalamus is considered to be the center that connects the neuroendocrine and immune systems. Echinacoside exerts neuroprotective effects through the neuroendocrine-immune network.

This is firs-human study of echinacoside in healthy subjects, and this is the first attempt to identify a population PK model for echinacoside. A one-compartment model with first-order elimination with AST as covariates was established. Our population pharmacokinetic model was built based on data obtained from single dose escalation and multiple dose escalation. The study with an intensive pharmacokinetic sampling design is ideal for attempting to identify the pharmacokinetic model structure of Naoqingzhiming tablets.

Our data showed that the one-compartment model more accurately described the pharmacokinetic features of Naoqingzhiming tablets. Therefore, a one-compartment model with time lag was finally selected as the basic model.

The goal of building the covariate model was to find subject-specific characteristics, which could explain, and thus reduce, the variability of the model. We tested the effect of 8 covariates, including age, gender, weight, BMI, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr) and total bilirubin (TBIL) on PK parameters. Finally, AST showed a significant effect on the PK model. The metabolism of echinacoside is currently only studied in animals. Echinacoside is absorbed in the gastrointestinal tract of rats and eliminated by the liver [18]. We speculate that echinacoside is also eliminated by the liver in the human body. The specific elimination method can be further studied.

Vascular dementia is a neurodegenerative disease. Studies have shown that the main pathological changes are vascular disease and white matter damage [19]. Animal experiments confirmed that echinacoside can penetrate the blood-brain barrier of rats [20]. The study only evaluated human pharmacokinetics and pharmacokinetic models. It is necessary to further develop the pharmacokinetic-pharmacodynamics (PKPD) model in the follow-up study of vascular dementia patients to evaluate the dose-effect relationship of Naoqingzhiming tablets.

There was fewer covariate effect in the PK model may be due to the nature of the subjects enrolled in the study. This was a phase I study conducted on healthy subjects, which was a uniform population with a relatively narrow range of covariates. The extrapolation of the model developed in this study need further evaluation in a larger number of subjects and patients with vascular dementia before the model can be fully validated.

Conclusion

This was the first population pharmacokinetic study for Naoqingzhiming tablets in the Chinese subjects. The population PK described by a one-compartment model with first-order absorption and linear elimination plus lag time. Of all of the evaluated covariates, only hepatic function (characterized by aspartate aminotransferase) is considered a clinically relevant factor.

Declarations

Funding

This work was supported by grants from the National Science and Technology Major Project of China for “Significant New Drugs Development” (2020ZX09201-018, 2017ZX09304-024) and Natural science foundation of Shandong province (ZR2019MH101).

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

The authors are grateful to Beijing Scrianen Pharmaceutical Co., Ltd., China, for their supports.

Reference

1. Llibre Rodriguez, J. J., Ferri, C. P., & Acosta, D., et al. (2008). Prevalence of dementia in Latin America, India, and China: a population-based cross-sectional survey. *Lancet (London, England)*, *372*(9637), 464–474. https://doi.org/10.1016/S0140-6736(08)61002-8
2. Wimo, A., Winblad, B., & Jönsson, L. (2010). The worldwide societal costs of dementia: Estimates for 2009. Alzheimer's & dementia: the journal of the Alzheimer's Association, 6(2), 98–103. https://doi.org/10.1016/j.jalz.2010.01.010
3. Wolters, F. J., & Ikram, M. A. (2019). Epidemiology of Vascular Dementia. Arteriosclerosis, thrombosis, and vascular biology, 39(8), 1542–1549. https://doi.org/10.1161/ATVBAHA.119.311908
4. Korczyn A. D. (2002). The complex nosological concept of vascular dementia. Journal of the neurological sciences, 203-204, 3–6. https://doi.org/10.1016/s0022-510x(02)00251-4
5. Sinha, K., Sun, C., Kamari, R., et al. (2020). Current status and future prospects of pathophysiology-based neuroprotective drugs for the treatment of vascular dementia. Drug discovery today, 25(4), 793–799. https://doi.org/10.1016/j.drudis.2020.01.003

6. Farooq, M. U., Min, J., Goshgarian, C., et al. (2017). Pharmacotherapy for Vascular Cognitive Impairment. CNS drugs, 31(9), 759–776. https://doi.org/10.1007/s40263-017-0459-3
7. Song, Y., Zeng, K., Jiang, Y., et al. (2021). Cistanches Herba, from an endangered species to a big brand of Chinese medicine. Medicinal research reviews, 41(3), 1539–1577. https://doi.org/10.1002/med.21768
8. Deng, M., Zhao, J. Y., Tu, P. F., et al. (2004). Echinacoside rescues the SHSY5Y neuronal cells from TNFalpha-induced apoptosis. European journal of pharmacology, 505(1-3), 11–18. https://doi.org/10.1016/j.ejphar.2004.09.059
9. Feng, X. Y., Zhu, M., Zhang, Q. Q., et al. (2012). Selective protection of nigral dopaminergic neurons by echinacoside in a rat model of Parkinson disease induced by rotenone. Zhong xi yi jie he xue bao = Journal of Chinese integrative medicine, 10(7), 777–783. https://doi.org/10.3736/jcim20120708
10. Wei, L. L., Chen, H., Jiang, Y., et al. (2012). Effects of echinacoside on histio-central levels of active mass in middle cerebral artery occlusion rats. Biomedical and environmental sciences: BES, 25(2), 238–244. https://doi.org/10.3967/0895-3988.2012.02.017
11. Brendel, K., Dartois, C., Comets, E., et al. (2007). Are population pharmacokinetic and/or pharmacodynamic models adequately evaluated? A survey of the literature from 2002 to 2004. Clinical pharmacokinetics, 46(3), 221–234. https://doi.org/10.2165/00003088-200746030-00003
12. Plassman, B. L., Langa, K. M., Fisher, G. G., et al. (2007). Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology, 29(1-2), 125–132. https://doi.org/10.1159/000109998
13. Chan, K. Y., Wang, W., Wu, J. J., et al. Global Health Epidemiology Reference Group (GHERG) (2013). Epidemiology of Alzheimer's disease and other forms of dementia in China, 1990-2010: a systematic review and analysis. Lancet (London, England), 381(9882), 2016–2023. https://doi.org/10.1016/S0140-6736(13)60221-4
14. Kalaria, R. N., Maestre, G. E., Arizaga, R., et al. (2008). Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. The Lancet. Neurology, 7(9), 812–826. https://doi.org/10.1016/S1474-4422(08)70169-8
15. Korczyn, A. D., Vakhapova, V., & Grinberg, L. T. (2012). Vascular dementia. Journal of the neurological sciences, 322(1-2), 2–10. https://doi.org/10.1016/j.jns.2012.03.027
16. Liu, J., Yang, L., Dong, Y., et al. (2018). Echinacoside, an Inestimable Natural Product in Treatment of Neurological and other Disorders. Molecules (Basel, Switzerland), 23(5), 1213. https://doi.org/10.3390/molecules23051213
17. Fu, Z., Fan, X., Wang, X., et al. (2018). Cistanches Herba: An overview of its chemistry, pharmacology, and pharmacokinetics property. Journal of ethnopharmacology, 219, 233–247. https://doi.org/10.1016/j.jep.2017.10.015
18. Jia, C., Shi, H., Jin, W., et al. (2009). Metabolism of echinacoside, a good antioxidant, in rats: isolation and identification of its biliary metabolites. Drug metabolism and disposition: the biological fate of chemicals, 37(2), 431–438. https://doi.org/10.1124/dmd.108.023697
19. Kalaria R. N. (2018). The pathology and pathophysiology of vascular dementia. Neuropharmacology, 134(Pt B), 226–239. https://doi.org/10.1016/j.neuropharm.2017.12.030
20. Wen, Y., Huo, S., Zhang, W., , et al. (2016). Pharmacokinetics, Biodistribution, Excretion and Plasma Protein Binding Studies of Acteoside in Rats. Drug research, 66(3), 148–153. https://doi.org/10.1055/s-0035-1555896