BMC Pharmacology and Toxicology

RESEARCH Open Access

Food effects and pharmacokinetic evaluation of oral single-dose prednisone acetate and prednisolone in healthy Chinese subjects

Baole Cai[1], Lingjun Li[1*], Pengcheng Ma[1*], Lei Tao[1], Jun Wei[1], Hongyang Li[1], Zhujun Shao[1], Yumin Yao[1], Yindi Zhong[1] and Yibing Li[1]

Abstract

Background To assess the food effects and pharmacokinetic profile of oral prednisone (test preparation,5 mg) and prednisolone tablets (reference preparation,5 mg) using a randomized, two-period, two crossover, single-dose, fast and fed trial in 48 (24 in fast, 24 in fed) healthy Chinese adult subjects.

Materials and methods In the trial, the plasma concentrations were determined at different time points up to 24 h and the pharmacokinetic parameters were analyzed according to the concentration data by non-compartmental analysis using WinNonlin software. All laboratory parameters, vital signs and adverse events (AEs) were monitored and recorded under the supervision of the clinicians throughout the whole process of the study.

Results Prednisone and prednisolone undergo interconversion in liver. On average, the bioavailability of prednisolone after oral prednisone is approximately 80% of that after prednisolone. And about 20% of prednisolone is converted to prednisone after administration of equivalent oral of prednisolone tablet. Food taken with prednisone or prednisolone tablets delays the time reach the peak prednisone or prednisolone concentration (T_{max}) by approximately 0.5 h but does not affect systemic exposure. Prednisone and prednisolone tablets were well tolerated, and there were no serious adverse events reported in the study.

Conclusions For there was no information about the pharmacokinetic profile and food effects of oral prednisone and prednisolone tablets, the result of this research would be a clinical medication for doctors especially dealing patients with varying degrees of liver diseases.

Clinical Trial Registration CTR20200093; registered in http://www.chinadrugtrials.org.cn/ at 11 March 2020.

Key points

• The food effects and pharmacokinetic evaluation of prednisone acetate and prednisolone were investigated in healthy Chinese subjects.

*Correspondence:
Lingjun Li
lljade@163.com
Pengcheng Ma
mpc815@163.com

Full list of author information is available at the end of the article

• Prednisone and prednisolone undergo interconversion in liver. On average, the bioavailability of prednisolone after oral prednisone is approximately 80% of that after prednisolone.
• Food taken with prednisone or prednisolone tablets delays the T_{max} but does not affect AUC.

Keywords Prednisone, Prednisolone, Pharmacokinetics, Food effects

Introduction

Prednisone is a commonly prescribed glucocorticosteroid which are widely used as anti-inflammatory, anti-allergic, anti-rheumatic for allergic and autoimmune inflammatory diseases [1].

Prednisone acetate is a kind of acetate of prednisone and prednisone's acetate formation increases the stability of prednisone. It is a unique component in China.

Prednisone acetate is more readily absorbed by the gastrointestinal tract and can be rapidly hydrolyzed to prednisone in the body. In vivo, prednisone has no physiological activity but prednisone can convert to prednisolone which is assumed to be the pharmacologically active component and prednisolone can convert to prednisone. So prednisone is a pro-drug and inactive metabolite of prednisolone [2].

But there is a poor understanding of the clinical role of its pharmacokinetics, especially owing to its unusual time course and nonlinear disposition. The absorption rate and degree especially the unusual interconversion bioavailability ratio of prednisone and prednisolone and food effect of the two drugs are not available in the drug instructions and still poor understanding [3].

Determining a drug's bioavailability and bioequivalence is important for measuring a drug's pharmacokinetic profile in biological matrices, and making important decisions regarding safety and efficacy.

In order to evaluate the food effects and pharmacokinetic profile of prednisone and prednisolone, a total of two randomized, two-period, crossover, fast and fed trials after a single oral of 5 mg prednisone (test preparation) and prednisolone (reference preparation) tablets in healthy Chinese subjects were carried out successively.

Methods

Study overview

The study protocol was approved by the Ethics Committee of the Hospital of Dermatology, Chinese Academy of Medical Sciences & Peking Union Medical College (Nanjing, China) successively and performed according to current revision of the Declaration of Helsinki and the GCP guideline. After having received a thorough informed about the aim, course and possible risks of the clinical trial, all subjects signed informed consent forms before their participation in the study.

In the trial, the reference preparation (R, 5 mg prednisolone tablet, Prednisolone Pfizer®) was product by Pfizer AB Corp (USA). The test preparation (T,5 mg prednisone tablet) was provided by Zhejiang Xianju Pharm Co., Ltd. (China).

Subjects

According to the statistical power analysis results, the sample size of 24 subjects is adequate for detecting the pharmacokinetic parameters of prednisone or prednisolone at fast or fed states. So a total of 48 subjects entered the trial.

All 48 male and female subjects were in good health after being assessed medical and drug abuse history, physical examination (neck, liver, nervous system, chest, spleen, blood pressure, pulse, body temperature, breathing), standard laboratory test results (standard hematology, blood chemistry, urinalysis),12-lead Electrocardiograms (ECGs), woman pregnancy test and drug abuse test(3,4-methylenedioxymethamphetamine, morphine, methylamphetamine, ketamine). Virus and Treponema pallidum screening was performed including Hepatitis B surface antigen, Hepatitis C antibody, Human immunodeficiency virus antibody and the gelatin agglutination of Treponema pallidum test. The prothrombin test was also carried out as a part of laboratory tests.

Volunteers whose screening results were clinically significant abnormal at physical examination, laboratory tests or ECGs were excluded. The following reasons were also served as exclusion criteria: a history of clinically significant cardiovascular, hepatic, renal, gastrointestinal, pulmonary, vascular diseases; a history of a psychiatric disorder; a history of alcohol abuse; allergy to the study drugs; participation in another clinical drug trial within the previous one month; blood donation within the previous 3 months; use any medication during the previous 2 weeks and women during breastfeeding period. Only subjects with all examination results being normal or abnormal with no clinical significance were enrolled the trial.

Study design and procedures

The trial was a single-dose (5 mg), randomized, two-period, crossover studies and carried out successively in the phase I clinical ward of the Hospital of Dermatology, Chinese Academy of Medical Sciences.

During the fast experimental phase, the participants entered into the ward one day before the trial. After a series of screening procedures including alcohol test and health consultations, the final 24 enrollment subjects were confirmed according to the inclusion and exclusion

criteria. The subjects were divided into two groups (12 in T group and 12 in R group at fast or fed trial) according to the random table by using SAS 9.4 software. Each subject was administered drug along with 240 mL of water. All doses were taken in the morning after an overnight fast. Subjects could drink water freely at 1 h and have standardized meals at 4 h and 10 h after drug administration. The strenuous exercises or bed ridden for subjects were forbidden. In each period, the volunteers should not leave the clinical ward. After one week of washout interval, the second period was repeated in the same procedure except the crossover drug. At the end of each period, blood cell count, blood biochemistry, urinalysis and ECGs were reexamined and the subjects could leave the ward.

During the fed experimental phase, the 24 subjects were given a high-fat breakfast (2 fried chicken hamburgers, 10 gram of butter and 250 ml of whole milk) half an hour before orally administration of drug according to the random table. The blood samples were also collected at the same time points. The other process of study was the same as the fast experimental state. Every period washout interval was one week. The second period followed the same procedure as the first one except the cross drug. The subjects could not leave the ward at each end of period until the laboratory tests and ECGs had been reexamined.

Analysis method assessments

Venous blood samples were collected pre-dose and post-dose at 0.25, 0.5, 0.75, 1, 1.33, 1.66, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12 and 24 h. At each time point, the blood volume was 4 mL. The plasma samples were centrifuged and separated at 2000 × g for 10 min and stored at -60 °C until LC-MS/MS analysis.

Prednisone and prednisolone were purchased from National Institutes for Food and Drug Control and prednisone-d8 was used as internal standard (I.S.,Toronto Research Chemicals) for the quantification.

The analysis of the plasma samples was conducted in Nanjing Clinical Tech Laboratories Inc. The Analysis of the concentrations of prednisone and prednisolone in plasma was performed with a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) equipped in a positive ion electrospray ionization. The LC-MS/MS system equipped with a Shimadzu LC-30AD HPLC system (Shimadzu, Japan) and an API 5500 mass spectrometer (Applied Biosystems, USA) with an electrospray ionization (ESI) interface operated in a multiplereaction monitoring (MRM) positive ion mode. Selected ion transitions were m/z 359.1(parent ion) to 265.0(product ion) for prednisone, m/z 361.1 (parent ion) to 325.1 (product ion) for prednisolone and m/z 367.2 (parent ion) to 270.2 (product ion) for internal standard (IS), respectively. An ACE C_{18} column combined with a guard column was used. The total analysis time was 5 min. The mobile phase consisted of (A) 0.5% formic acid containing 5.00 mM NH_4Ac solution and (B) acetonitrile containing 0.1% formic acid (B). A gradient elution procedure was carried out as the following program: 0–1 min, 35% B; 1.1–2.7 min, 50% B; 2.8–3.5 min, 100% B; 3.6–5.0 min, 35% B in 5 min. The flow rate was set at 0.4 mL/ min.

The determination method was validated by carrying standard concentration curve of the two analytes, the intra- and inter-day precisions, the matrix effects and the stability experiments.

Fifty microliters of plasma sample was added to a 96-well plate. Then 30 μL of IS (120 ng/mL) and 30μL of 50% acetonitrile aqueous solution were added to all samples. After being vortexed 3 min and centrifuged at 4000 rpm for 10 min, the 120 μL supernatant was transferred into 96-well plate and diluted with 80 μL ultrapure water. Aliquot of 20 μL of each sample solution was injected for LC-MS analysis.

Pharmacokinetic assessments

The main pharmacokinetic parameters included the area under the plasma concentration-time profile from 0 to the last measurable concentration (AUC_{0-t}), AUC extrapolated from time zero to infinity ($AUC_{0-\infty}$), and the maximum plasma concentration (C_{max}) and the time required to reach C_{max} (T_{max}).

From the plasma concentration data, pharmacokinetic parameters could be estimated by non-compartmental analysis using WinNonlin Professional software (Pharsight Corp., Mountain View, CA, USA) (version 8.0).

The difference of T_{max} between prednisone and prednisolone was examined by t-test. The SAS software (SAS Institute Inc., Cary, NC, USA) (version 9.4) software was employed for the bioequivalence statistical analysis. Bioequivalence was determined as two-sided 90% confidence intervals (CI) and adjusted geometric mean ratios (GMRs) of the AUC and C_{max} for each constituent of test and reference preparation within 80.00–125.00%.

Safety assessments

All laboratory parameters, vital signs and adverse events (AEs) were monitored and recorded under the supervision of the clinicians throughout the whole process of the study. The ward was equipped with emergency rescue drugs and instruments.

Results

Subjects

After being screened as the same inclusion and exclusion criteria, a total of 24 healthy Chinese volunteers (15 males, 9 females, aged 24.58 ± 5.58 years,

Table 1 Baseline characteristics of the subjects at fast or fed state

Baseline characteristic	Fast (Mean ± SD)	Fed (Mean ± SD)
Gender, n (%)	Male 15(62.5); Female 9(37.50)	Male 16(66.67); Female 8(33.33)
Age (years)	24.58 ± 5.58	26.42 ± 5.01
Height (cm)	170.35 ± 6.84	168.94 ± 7.52
Weight (kg)	62.25 ± 8.54	61.78 ± 5.72
BMI (kg/m^2)	21.41 ± 2.30	21.66 ± 1.81
Ethnicity, n (%)	Han 23(95.83)	Han 24(100)

Table 2 The main laboratory examination parameters of the subjects at fast or fed state

Parameter	Fast (Mean ± SD)	Fed (Mean ± SD)
Blood white blood cells (10^9/L)	5.82 ± 1.17	6.32 ± 1.47
Blood red blood cells (10^12/L)	4.74 ± 0.50	4.79 ± 0.42
Hemoglobin (g/L)	145.75 ± 16.42	147.75 ± 10.48
Platelet (10^9/L)	234.67 ± 46.82	244.38 ± 51.03
Total Bilirubin (μmol/L)	12.52 ± 5.08	13.96 ± 3.65
Alaninetransaminase (U/L)	16.96 ± 10.18	18.04 ± 11.47
Aspartate aminotransferase (U/L)	19.58 ± 4.56	18.83 ± 5.04
Urea (mmol/L)	4.07 ± 0.86	3.89 ± 1.08
Creatinine (μmol/L)	64.21 ± 12.40	64.71 ± 12.45
Total cholesterol (mmol/L)	4.26 ± 0.68	4.04 ± 0.80

BMI 21.41 ± 2.30) and 24 healthy Chinese volunteers (16 males, 8 females, aged 26.42 ± 5.01 years, BMI 21.66 ± 1.81) were enrolled in the fast and the fed state of the trial, respectively (Table 1). The main laboratory examination parameters of the enrolled volunteers were shown in Table 2.

Analysis methodology result

The determination method was validated and found to be linear over the concentration range of 0.60 to 40 ng/mL (r^2 = 0.9938) for prednisone, 1.00 to 160 ng/mL (r^2 = 0.9947) for prednisolone. The LLOQ (lower limit of quantification) and ULOQ (upper limit of quantification) were 0.60 and 40 ng/mL for prednisone, 1.00 and 160 ng/mL for prednisolone respectively.

The intra- and inter-day precisions of the two analytes were acceptable (intra- and inter-day variation ≤ 16.2% for prednisone, ≤ 10.5% for prednisolone), and accuracy (recovery ≥ 90.4% for prednisone, ≥ 89.6% for prednisolone). The internal standard normalized matrix effect factors (IS-normalized MF) of the two analytes were all less than 15%.The accuracy results of the stability experiments were all less than 15% which showed that prednisone and prednisolone were all stable during short-term storage (at room temperature, 1 day), preparation storage (8 °C,7 day), five freeze - thaw cycles (-20 °C,-70 °C), and long-term storage (stored at -20 °C, -70 °C, 77 days).

The determination methodology results demonstrated that the method was rapid and reliable for simultaneous analysis prednisone and prednisolone. The chromatograms of prednisone and prednisolone were shown in Fig. 1 and 2.

Pharmacokinetic analysis

After administration of prednisone tablet, prednisone is converted in the liver to prednisolone, which is the major pharmacologically active metabolite of prednisone. Prednisolone can also convert to prednisone in plasma. In fast state, the mean plasma prednisone and prednisolone concentration-time profiles were shown in Figs. 3–6. The mean plasma prednisone and prednisolone concentration profiles obtained from both preparations were almost identical.

For prednisone component, the C_{max}, AUC_{0-t} and T_{max} were 23.59 ng/mL, 122.10 ng·h/mL and 3.50 h for the test preparation, whereas those for reference one were 25.00 ng/mL, 136.91 ng·h/mL and 3.0 h respectively at fast

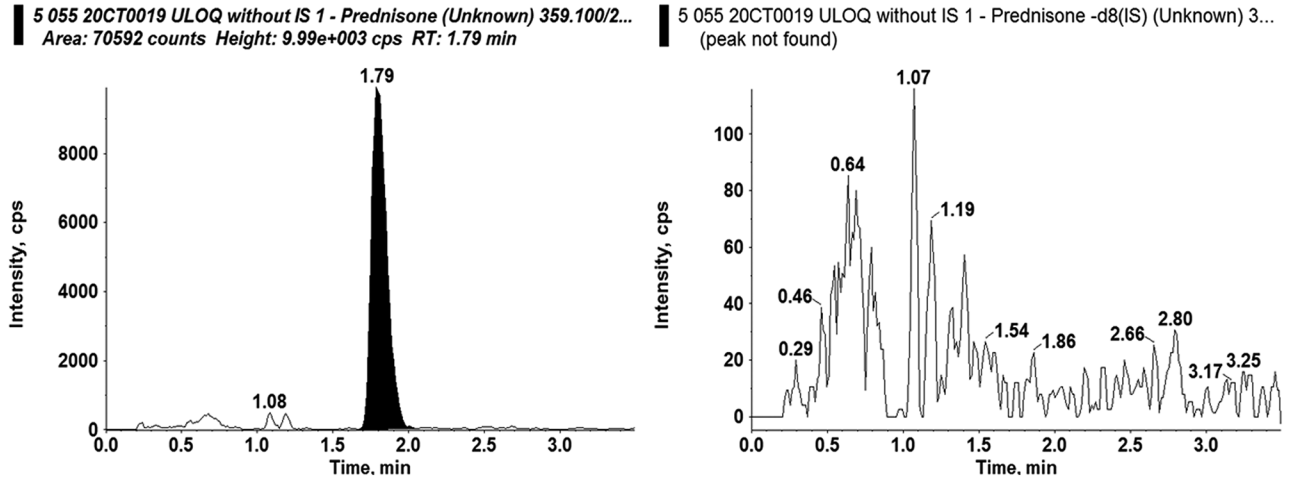

Fig. 1 The HPLC-MS/MS chromatogram of prednisone

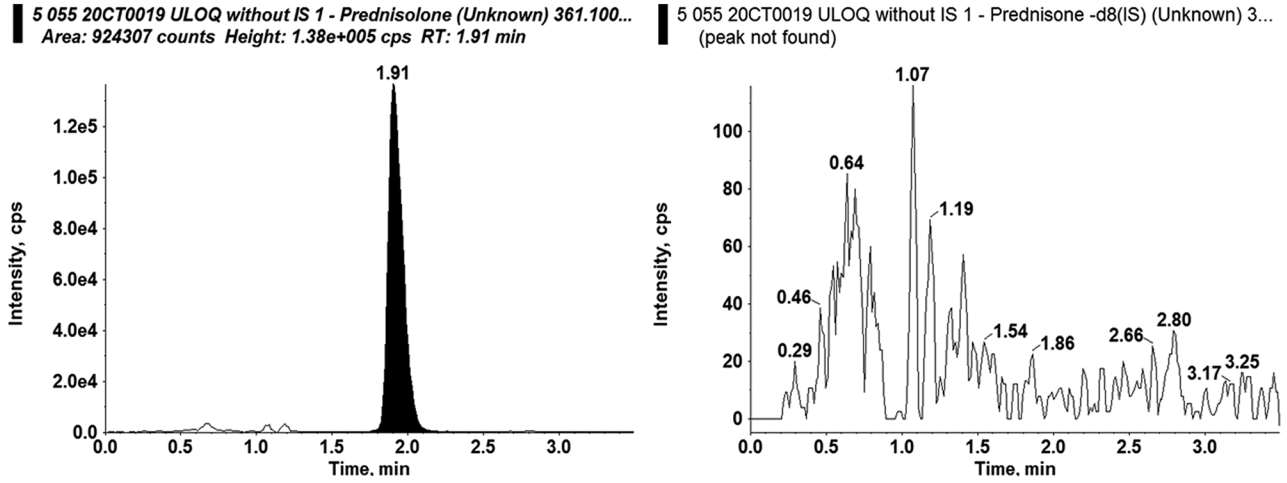

Fig. 2 The HPLC-MS/MS chromatogram of prednisolone

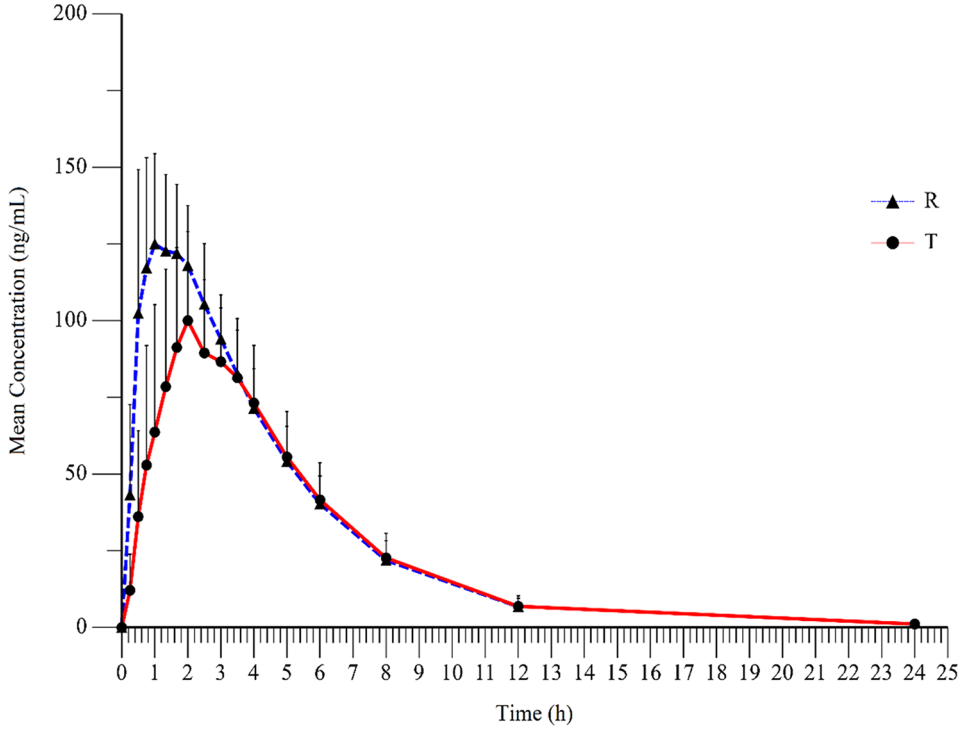

Fig. 3 The mean plasma concentration-time profile of prednisolone in fast study

state. For prednisolone component, the C_{max}, AUC_{0-t} and T_{max} were 118.05 ng/mL, 532.58 ng·h/mL and 1.84 h for the test preparation, whereas those for reference one were 140.79 ng/mL, 621.19 ng·h/mL and 1.0 h respectively at fast state (Table 3).

While in fed study, the C_{max}, AUC_{0-t} and T_{max} obtained from test preparation were 20.26 ng/mL,123.09 ng·h/mL and 4.0 h whereas those from reference one were 22.53 ng/mL,138.23 ng h/mL and 3.52 h, respectively for prednisone. The C_{max} and AUC_{0-t} obtained from test preparation were 109.35 ng/mL, 584.86 ng·h/mL and 2.50 h whereas those from reference one were 118.85 ng/mL, 666.30 ng h/mL, and 1.67 h respectively for prednisolone.

In fast or fed study, both drugs are rapidly absorbed after oral administration, reaching peak plasma concentrations after 1 to 4 h. The T_{max} of prednisone are longer (3.0–3.5 h in fast state, 3.52–4.0 h in fed state) than that of prednisolone (1.0–1.84 h in fast state, 1.67–2.50 h in fed state) ($P < 0.01$).

In conclusion, the pharmacokinetic parameters were similar between prednisone and prednisolone. Whatever in the fast or fed study, the 90% CIs of the GMRs

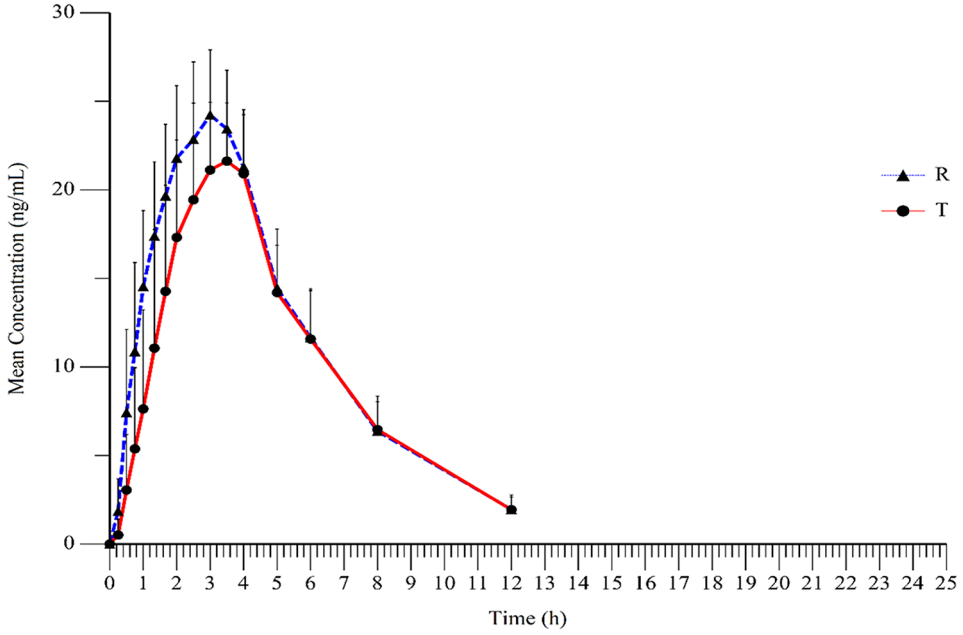

Fig. 4 The mean plasma concentration-time profile of prednisone in fast study

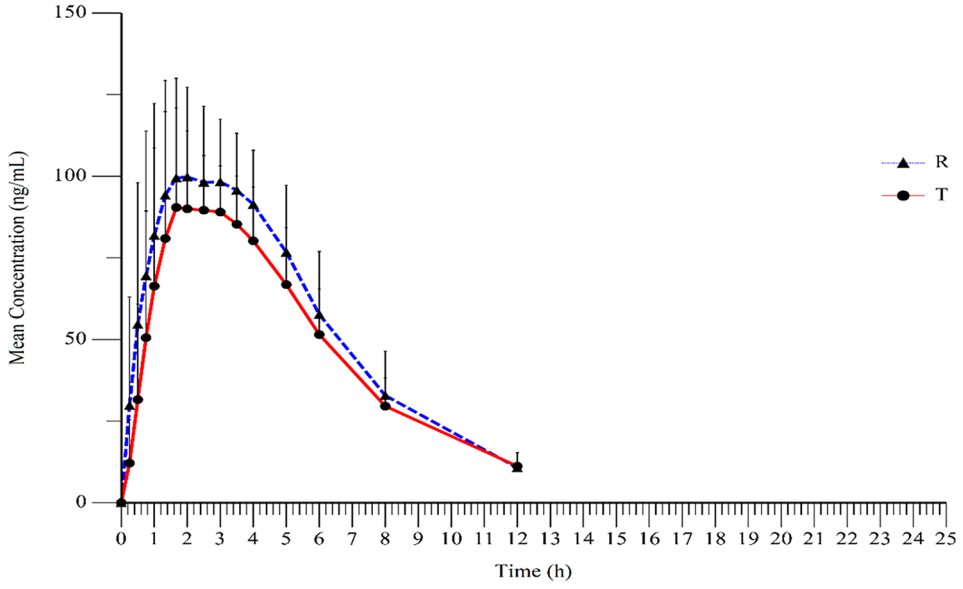

Fig. 5 The mean plasma concentration-time profile of prednisolone in fed study

of prednisone and prednisolone for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$are within the bioequivalence acceptance range of 80.00-125.00%, indicating that prednisone and prednisolone are bioequivalent (Table 4).

Safety analysis

In the trials, the 5 mg of prednisone or prednisolone was safe and well tolerated in fast and fed state, and there were no serious AE reported in the two studies. The laboratory abnormalities or clinically significant changes in vital signs or ECGs were mild (Table 5). At last, a total of 21 subjects have completed the fast study and a total of 23 subjects have finished the fed trial. Three subjects in fast stage and one subject in fed stage dropped out in the first period for adverse events.

Discussion

In vivo, prednisolone and prednisone undergo reversible inter-conversion metabolism mediated primarily by type 1 dehydrogenase (11β-HSD) and type 2 dehydrogenase (11β-HSD2) in liver. 11β-HSD1 acts primarily as a reductase transforming inactive prednisone to active

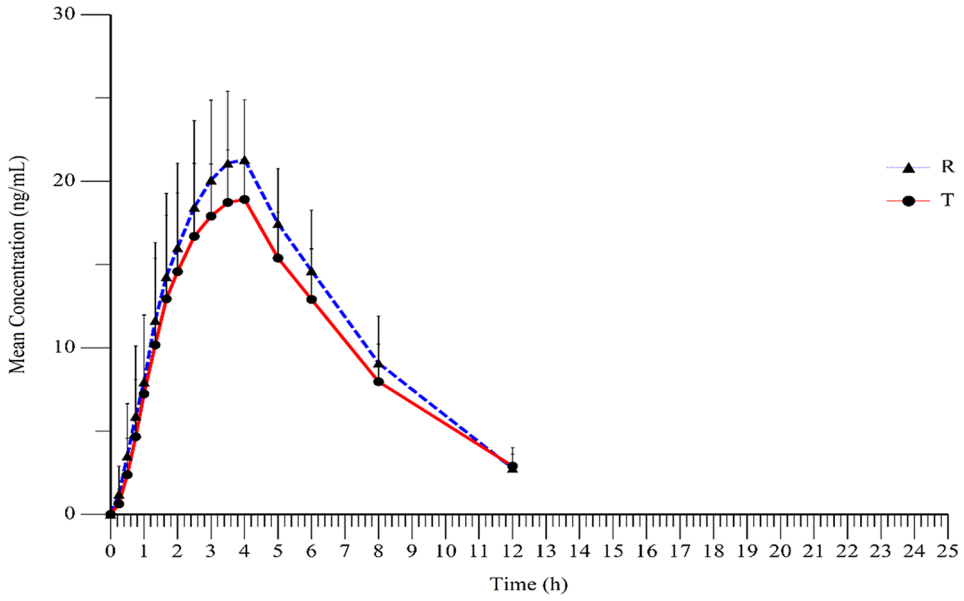

Fig. 6 The mean plasma concentration-time profile of prednisone in fed study

prednisolone, while 11β-HSD2 acts primarily as an oxidase transforming active prednisolone to inactive prednisone [4, 5]. The metabolic inter-conversion of prednisone and prednisolone is nonlinear metabolic conversion which has been related to nonlinear plasma protein binding [6, 7]. That is to say, prednisone and prednisolone can interconvert in plasma after taken with prednisone or prednisolone tablets.

But the unusual pharmacokinetic course and food effect of the two drugs are not available in the drug instructions and can´t meet the needs of dose adjustment during clinical use. In order to improve the drug instruction with supplementary information, a total of two randomized, two-period, crossover, fast and fed trials after a single oral of 5 mg prednisone and prednisolone tablets in healthy Chinese subjects were carried out to evaluate the food effects and pharmacokinetic profiles of prednisone and prednisolone. After a series of screening procedures, a total of 48 enrollment subjects (24 in fast group, 24 in fed group) were enrolled in the trial. According to the statistical power analysis results, prednisone and prednisolone all have small coefficients of intra-individual variation in healthy volunteers. So the sample size of 24 subjects is adequate for detecting the differences in pharmacokinetic parameters between different subjects at fast or fed states.

In fast study, the C_{max} of prednisone component in plasma was not significantly different between test and reference preparations, but AUC_{0-t} of prednisone in test preparation was significantly less than that of in reference one. While for the prednisolone component, there were significant differences in C_{max} and AUC_{0-t} parameters of prednisolone between the test and reference preparations. The results showed that the C_{max} and AUC_{0-t} of prednisolone in the test one were lower than in the reference one.

In fed condition, the results suggested that the C_{max} and AUC_{0-t} of prednisone and prednisolone in plasma were significantly different between the two groups. The C_{max} and AUC_{0-t} of prednisone and prednisolone of the test preparation were lower than those of the reference preparation.

The plasma concentration of prednisolone was about 5 times that of prednisone after either administration of test or reference preparation under fast or fed state.

Interestingly, the mean plasma concentration ratios of prednisone and prednisolone were very similar whatever administration of prednisone and prednisolone tablet in fast or in fed state. Prednisone or prednisolone was converted into prednisolone or prednisone immediately. At 0.25 h, the concentration ratio of prednisone/prednisolone was about 3%. With time going on, the concentration of prednisone increases. And the maximum ratio was about 30% happened at 4 h in fast state and about 28% happened at 8 h in fed state. The mean plasma concentration ratios of prednisone and prednisolone were shown in Fig. 7.

There is a high degree of interconversion between prednisone and prednisolone. On average, the comparison of AUC of prednisone or prednisolone showed that approximately 82% (81.20% of fast,82.59% of fed) of prednisone is converted to prednisolone after administration of 5 mg of prednisone tablet and about 18% (18.11% of fast,17.16% of fed) of prednisolone is converted to prednisone after administration of equivalent oral of prednisolone tablet.

Table 3 Mean pharmacokinetic parameters of prednisone and prednisolone in T and R formulations at fast or fed state

Parameter	Fast (Mean ± SD)				Fed (Mean ± SD)			
	prednisolone		prednisone		prednisolone		prednisone	
	T (n = 22)	R (n = 22)	T (n = 22)	R (n = 22)	T (n = 23)	R (n = 23)	T (n = 23)	R (n = 23)
C_{max} (ng/mL)	118.05 ± 19.19	140.79 ± 28.00	23.59 ± 3.68	25.00 ± 3.48	109.35 ± 26.74	118.85 ± 17.45	20.26 ± 2.89	22.53 ± 3.19
AUC_{0-t}(ng·h/mL)	532.58 ± 97.57	621.19 ± 89.85	122.10 ± 17.22	136.91 ± 19.54	584.86 ± 77.53	666.30 ± 91.10	123.09 ± 14.28	138.23 ± 18.92
$AUC_{0-\infty}$(ng·h/mL)	553.61 ± 101.96	644.61 ± 98.29	128.98 ± 19.50	143.65 ± 21.63	630.41 ± 85.54	705.30 ± 104.27	134.09 ± 17.11	148.35 ± 21.13
$t_{1/2}$ (h)	2.30 ± 0.31	2.29 ± 0.28	2.32 ± 0.39	2.32 ± 0.29	2.72 ± 0.42	2.46 ± 0.29	2.79 ± 0.56	2.50 ± 0.28
T_{max}* (h)	1.84(1.00 ~ 3.50)	1.00(0.50 ~ 2.00)	3.50(1.33 ~ 4.00)	3.00(1.67 ~ 3.50)	2.50(0.75 ~ 5.00)	1.67(0.25 ~ 5.00)	4.00(2.50 ~ 6.00)	3.52(2.50 ~ 5.00)

*median (minimum, maximum)

Table 4 The GMR and 90% CI of prednisone and prednisolone in T and R formulations at fast or fed state

Parameter	Fast (GMR)								Fed (GMR)							
	prednisolone				prednisone				prednisolone				prednisone			
	T	*R*	T/*R* (%)	90%CI(%)	T	*R*	T/*R* (%)	90%CI(%)	T	*R*	T/*R* (%)	90%CI(%)	T	*R*	T/*R* (%)	90%CI(%)
C_{max}(ng/mL)	116.69	138.17	84.46	(80.30 ~ 88.83)	23.35	24.65	94.71	(89.55 ~ 100.16)	106.59	117.78	90.50	(84.06 ~ 97.43)	20.08	22.30	90.04	(87.11 ~ 93.08)
AUC_{0-t} (ng·h/mL)	521.40	609.52	85.54	(83.46 ~ 87.68)	120.75	134.78	89.59	(85.55 ~ 93.82)	580.27	661.77	87.68	(86.04 ~ 89.36)	122.31	137.10	89.22	(86.97 ~ 91.52)
AUC_{0-inf}(ng·h/mL)	541.22	631.44	85.71	(83.71 ~ 87.76)	127.24	141.21	90.11	(86.02 ~ 94.39)	625.41	699.95	89.35	(87.35 ~ 91.40)	132.37	147.11	89.98	(86.71 ~ 93.38)

Table 5 Adverse events of prednisone and prednisolone in T and R formulations at fast or fed state

Adverse events	Fast		Fed		Severity
	T (n = 23)	R (n = 22)	T (n = 23)	R (n = 23)	
Alanine aminotransferase increased	2(8.70%)	1(4.55%)	0	0	Mild
Bilirubin increased	0	1(4.55%)	0	0	Mild
Urine white blood cells increased	1(4.35%)	1(4.55%)	0	0	Mild
Urine red blood cells increased	1(4.35%)	0	0	0	Mild
Blood glucose increased	0	1(4.55%)	0	0	Mild
Blood pressure decreased	1(4.35%)	0	0	0	Mild
Electrocardiogram abnormal	0	1(4.55%)	1(4.35%)	1(4.35%)	Mild
Urine latent blood	0	0	1(4.35%)	0	Mild
Dizzy	0	0	0	1(4.35%)	Mild

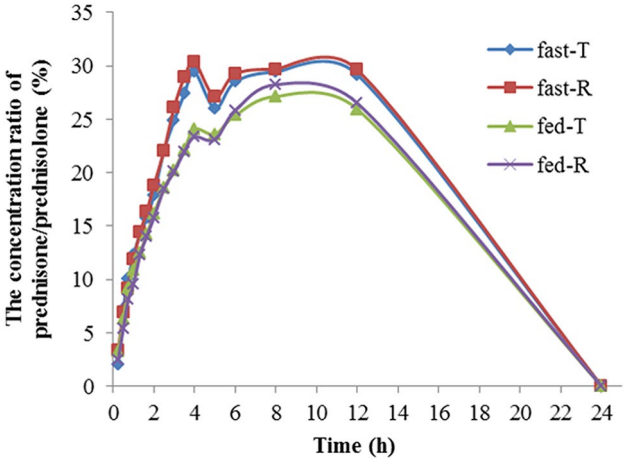

Fig. 7 The mean plasma concentration ratios of prednisone and prednisolone

Food had no effect on the extent of absorption (AUC_{0-t} 122.10, 136.91 [fast, T,R] vs. 123.09, 138.23 ng·h/mL [fed, T,R] of prednisone, AUC_{0-t} 532.58, 621.19 [fast, T,R] vs. 584.86, 666.30 ng·h/mL [fed, T,R] of prednisolone), and peak concentration was not significantly changed (C_{max} 23.59, 25.00 [fast, T,R] vs. 20.26, 22.53 ng/mL [fed, T,R] of prednisone, C_{max} 118.05,140.79 [fast, T,R] vs. 109.35,118.85 ng/mL [fed, T,R] of prednisolone), while rate of absorption was slow down after the high-fat food (T_{max} 3.50, 3.00 [fast, T,R] vs. 4.00, 3.52 h [fed, T,R] of prednisone, 1.84, 1.00 [fast, T,R] vs. 2.50, 1.67 h [fed, T,R] of prednisolone).

Food taken with test or reference tablets did not affect bioavailability, except delayed the time required to reach the peak prednisolone or prednisolone concentration (T_{max}) approximately 0.5 h.

In addition to the impact of liver function on pharmacokinetics, kidney function could also affect drug metabolism of prednisone or prednisolone. Moreover, the pharmacokinetic behaviors in special populations such as the older adults and women during pregnancy and lactation were also different [8–10].

The administration of drugs in fed state reduced the absorption rate of prednisone and prednisolone, which was consistent with the research results of Al-Habet and Rogers [11]. However, the delayed time was not same due to different ethnicities, sample size and drug formulations.

Conclusions

In conclusion, prednisone was bioequivalent and as safe as prednisolone under fast or fed conditions in healthy Chinese subjects.

The ingestion of food did not increase the extent of prednisone or prednisolone absorption. Therefore if concern regarding upper gastrointestinal side effects, it can be recommended to patients that prednisone or prednisolone be taken with a meal.

Liver disease decreased the conversion ratio of prednisone to prednisolone. At the same time, it prolongs the prednisolone half-life in such patients. The reduced plasma concentration of prednisolone can be partially compensated for by delayed clearance.

Thus, there is little advantage of one preparation over the other.

Because prednisone has no physiological activity but prednisolone is a pharmacologically active component in vivo, prednisolone has more clinical advantages than prednisone. In gerenal, prednisolone may be a more suitable option for patients in clinical use than prednisone due to its direct administration. It is important to consider the severity of liver dysfunction and the specific clinical physical conditions when making treatment decisions.

Acknowledgements
We are grateful to Zhejiang Xianju Pharm Co., Ltd. and Nanjing Clinical Tech Laboratories Inc.

Author contributions
BLC and LJL wrote the manuscript text. LJL, PCM and BLC participated in clinical trial protocols design. LT, JW, HYL, ZJS, YMY, YDZ and YBL performed research. All authors read and approved the final manuscript.

Funding
This study was funded by Zhejiang Xianju Pharm Co., Ltd.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of the Hospital of Dermatology, Chinese Academy of Medical Sciences & Peking Union Medical College (Nanjing, China).All subjects signed informed consent forms before their participation in the study after having received a thorough informed about the aim, course and possible risks of the clinical trial.

Consent for publication
All authors read and approved the final manuscript for publication.

Competing interests
The authors declare no competing interests.

Author details
[1]Hospital of Skin Diseases and Institute of Dermatology, Chinese Academy of Medical Sciences & Peking Union Medical College, Nanjing, Jiangsu 210042, China

Received: 30 July 2024 / Accepted: 3 February 2025
Published online: 17 February 2025

References

1. Rees AD, Merke DP, Arlt W, de la Brac A, Linden-Hirschberg A, Juul A et al. Comparison of modified-release hydrocortisone capsules versus prednisolone in the treatment of congenital adrenal hyperplasia. Endocr Connections. 2024 Jun 1.
2. Bergmann TK, Barraclough KA, Lee KJ, Staatz CE. Clinical pharmacokinetics and pharmacodynamics of prednisolone and prednisone in solid organ transplantation. Clin Pharmacokinet. 2012;51(11):711–41.
3. Zhang KY, Duan WW, Luo YB, Li Y, Hu J, Yang H. Comparative effectiveness and safety of intravenous methylprednisolone and tacrolimus monotherapy in ocular myasthenia gravis with unsatisfactory prednisone responses: a retrospective study. 2024;19(1):19.
4. Czock D, Keller F, Rasche FM, Häussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. Clin Pharmacokinet. 2005;44(1):61–98.
5. Diederich S, Eigendorff E, Burkhardt P, Quinkler M, Bumke-Vogt C, Rochel M, et al. 11beta-hydroxysteroid dehydrogenase types 1 and 2: an important pharmacokinetic determinant for the activity of synthetic mineralo- and glucocorticoids. J Clin Endocrinol Metab. 2002;87(12):5695–701.
6. Li X, DuBois DC, Almon RR, Jusko WJ. Physiologically based pharmacokinetic modeling involving nonlinear plasma and tissue binding: application to Prednisolone and Prednisone in rats. J Pharmacol Exp Ther. 2020;375(2):385–96.
7. Huang ML, Jusko WJ. Nonlinear pharmacokinetics and interconversion of prednisolone and prednisone in rats. J Pharmacokinet Biopharm. 1990;18(5):401–21.
8. Cossart AR, Isbel NM, Campbell SB, McWhinney B, Staatz CE. Does Age Influence immunosuppressant drug pharmacokinetics in kidney transplant recipients? Eur J Drug Metab Pharmacokinet. 2024;49(6):751–61.
9. Skauby RH, Gustavsen MT, Andersen AM, Bjerre A, Åsberg A, Midtvedt K, et al. Prednisolone and Prednisone Pharmacokinetics in Adult Renal Transplant recipients. Ther Drug Monit. 2021;43(2):247–55.
10. Ryu RJ, Easterling TR, Caritis SN, Venkataramanan R, Umans JG, Ahmed MS, et al. Prednisone Pharmacokinetics during pregnancy and lactation. J Clin Pharmacol. 2018;58(9):1223–32.
11. Al-Habet SM, Rogers HJ. Effect of food on the absorption and pharmacokinetics of prednisolone from enteric-coated tablets. Eur J Clin Pharmacol. 1989;37(4):423–6.

Publisher's note