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Original article

Bioequivalence evaluation of two formulations of pidotimod using a limited sampling strategy

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ABSTRACT

The aim of this study was to develop a limited sampling strategy (LSS) to assess the bioequivalence of two formulations of pidotimod. A randomized, two-way, cross-over study was conducted in healthy Chinese volunteers to compare two formulations of pidotimod. A limited sampling model was established using regression models to estimate the pharmacokinetic parameters and assess the bioequivalence of pidotimod. The model was internally validated by the Jack-knife method and graphical methods. The traditional non-compartmental method was also used to analyze the data and compared with LSS method. The results indicate that following oral administration of a single 800 mg dose, the plasma $AUC_{0-12\ h}$ and C_{max} of pidotimod can be predicted accurately using only two to four plasma samples. The bioequivalence assessment based on the LSS models provided results very similar to that obtained using all the observed concentration–time data points and indicate that the two pidotimod formulations were bioequivalent. A LSS method for assessing the bioequivalence of pidotimod formulations was established and proved to be applicable and accurate. This LSS method could be considered appropriate for a pidotimod bioequivalence study, providing an inexpensive cost of sampling acquisition and analysis. And the methodology presented here may also be applicable to bioequivalence evaluation of other medications.

1. Introduction

Pidotimod is an immunopotentiating agent. It cannot only stimulate non-specific immune reactions, but also can stimulate specific immune reactions. Previous studies have shown that pidotimod displays an immunopotentiating activity also on macrophages and granulocytes. Pidotimod is useful in increasing the immune defense during infections [1]. Pidotimod is often used in the treatment of recurrent respiratory infections (RRI) and may be rated as an excellent drug in the management of RRI in children [2]. The pharmacokinetics of the pidotimod after the absorption phase are not influenced by food. As a matter of fact, half-life and MRT do not differ significantly when the drug is taken after fasting or after a standard meal [3]. Previous studies showed that no differences in absorption, excretion and pharmacokinetic parameters have been evident between old and young volunteers. Patients with impaired renal function showed different pharmacokinetic parameters related to pidotimod with respect to the different grades of kidney function [4]. However, reports on the pharmacokinetics of pidotimod are relatively few in number [2,3].

On the other hand, limited sampling strategies (LSS), a type of statistical method, first put forward by Johnston A. et al., for therapeutic drug monitoring has been proven sufficiently robust for the accurate estimation of individual drug pharmacokinetics [5]. This quantitative methodology is very valuable, especially when sampling at "unsociable" hours is undesirable [6–8]. Pharmacokinetic parameters can be evaluated according to mathematical modeling based on the limited sampling points achieved. In previous study, we have successfully applied this quantitative methodology to precisely calculate the pharmacokinetic parameters of some medications, such as cefaclor and gliclazide [9,10].

In the present study, a bioequivalence study of pidotimod was conducted and the data were used to develop limited sampling strategy (LSS) models for estimating the area under the concentration–time curve (AUC) and the peak plasma concentration (C_{max}) of pidotimod. This study determines whether these LSS

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might be useful for bioequivalence evaluation of two formulations of pidotimod given to healthy volunteers. The application of LSS models in bioequivalence studies can reduce the cost of the sampling and analysis work of the medical staff. It may be potentially interesting if we explore a minimized BE study design with less sampling points.

2. Material and methods

2.1. Study subjects and methods

A bioequivalence study in which 20 healthy adult volunteers were enrolled. The concentrations of pidotimod in serum samples and the corresponding pharmacokinetic parameters were derived from this study. The study was conducted in accordance with the revised declaration of Helsinki and the rules of good clinical practice (ICH-GCP). The clinical protocol was approved by the Ethics Committee and all participants provided written informed consent.

Twenty male volunteers were selected according to their medical history, physical examination, electrocardiogram, and standard laboratory test results (blood cell count, biochemical profile, and urinalysis). These volunteers had not used any investigational drug during the preceding 6 months and prescription drugs were not permitted during the study. Their demographics are shown in Table 1.

Eligible participants were randomly assigned in a 1:1 ratio to receive 800 mg each of the dried-suspension (test) or granules (reference) formulation, followed by a 2-week washout period and administration of the alternate formulation. Thus all 20 enrolled volunteers received the reference formulation, whereas each generic formulation was administered to 20 volunteers. The pidotimod was administered with 200 ml water at 7:00 am after a 10-hour overnight fast. About 800 mg of the test product or reference product was administered as a single dose given orally under fasting conditions. Blood samples of 3 mL were withdrawn prior to administration as well as 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 20 hours after the intake of the drug. The whole blood samples were collected in heparinized tubes. The serum was separated within 30 minutes and stored at −20 °C. Pidotimod concentrations in the serum were analyzed by liquid chromatography-mass spectrometry (LC-MS) [11].

2.2. HPLC chromatographic analysis

About 10 μL of cefaclor standard solution (60 μg/mL) was added into 1.5 mL labeled microcentrifuged tubes and spiked 100 μL of plasma sample (respective concentration) into each tube and vortexed briefly. The mixture was precipitated with 200 μL methanol and vortexed briefly for about 3 min. Then the samples were centrifuged at 12,000 rpm for approximately 10 min at ambient temperature. A 100 μL aliquot of the supernatant was subsequently diluted with 100 μL deionized water. The resultant solution was then vortex-mixed for 1 min, centrifuged at 12,000 rpm for 5 min, and a 10 μL aliquot of the supernatant was directly injected onto the HPLC column.

Table 1
Demographics of the healthy volunteers ($n = 20$).

	Mean ± SD (Range)
Age (year)	23.0 ± 1.5 (18–26)
Height (cm)	175.0 ± 6.4 (163–186)
Weight (Kg)	68.2 ± 7.3 (53–80)
ALT (IU/L)	14.8 ± 9.0 (3–38)
Cr (μmol/L)	83.6 ± 11.6 (70–109)
BUN (mmol/L)	4.4 ± 0.8 (2.6–5.8)

The shimadzu LC/MS system consisted of a LC-20AD pump, a SIL-20AC auto sampler, a CTO-20A column oven and a LCMS-2010EV mass spectrometer equipped with an ESI source. The injection volume was 10 μL, with the column compartment at 30 °C. Chromatographic separation was performed by shimadzu VP-ODS column (250 mm × 2.0 mm, 3 μm), using the isocratic elution of 0.1% formic acid in methanol and water (33/67, v/v) at a flow-rate of 200 μL/min. The mass spectrometer was set to monitor pidotimod and cefaclor (IS) using selective ion monitoring (SIM) in the positive ion mode, with pidotimod and cefaclor detected at m/z of 245 and 369, respectively. Universal mass spectrometric settings included detector voltage of 1.65 kV, CDL temperature of 250 °C, heat block temperature of 200 °C.

2.3. Pharmacokinetic analysis

The value of C_{max} was determined from the individual concentration data. The non-compartmental model for extravascular input was used for calculation of the pharmacokinetic parameters AUC_{0-12h} (area under the drug concentration–time curve between 0 and 12 h, calculated by the trapezoidal rule) and extrapolated $AUC_{0-\infty}$ (AUC from 0 to infinity). The parameters thus obtained were used as the "best estimates" of parameter values.

2.4. Limited sampling strategies (LSS)

Twelve blood sampling times at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 h were taken for estimating $AUC_{0-12\ h}$. The formula is: $AUC_{0-12_t} = A_0 + A_1 \times C_1 + A_2 \times C_2 + \cdots + A_n \times C_n$, where C_n and A_n refer to the n^{th} blood sampling points and coefficients for modeling respectively. We select the 1, 2, 3, 4 points respectively as a limited sampling from those 12 points and substitute them into the formula above to estimate the $AUC_{0-12\ h}$ All of the possible assembled numbers are $561 = C_{11}^1 + C_{11}^2 + C_{11}^3 + C_{11}^4$, that is 561 regression equations in total. All of the regression coefficients were computed and ordered according to the determination coefficient r^2 and the number of parameters, where r^2 is an important parameter for assessing the model quality. The first-order Jack-knife was adopted to test and confirm the model [12,13]. One case is removed from the total of 40 cases each time. The remaining 39 cases serve as a Jack-knife sample which is used to calculate the fitting parameter of the regression equations. Then the regression equations are used to estimate the case initially removed. All of the cases are ergodic and obtained 40 results. Absolute predict error (APE) and Root mean square error (RMSE) were used to evaluate the model:

$$APE(\%) = (|Pred - Obs|)/Obs \times 100\% \quad (1)$$

$$RMSE = \sqrt{(1/N) \times \sum (APE)^2} \times 100\% \quad (2)$$

where Pred is the predicted value of the LSS model, and Obs is the trapezoidal summation value.

In addition, a B-A plot of the predicted value and Obs value were plotted, with the Obs value ±10% and 15% as the reference line [14]. The calculations above were achieved through the EXCEL-VBA program. The mountain plot analysis is also very useful for visualization [15], which tests the agreement between two-estimated $AUC_{0-12\ h}$ and C_{max}.

2.5. Bioequivalence assessment

The 90% confidence interval (CI90%) of the individual radio (test formulation/reference formulation) of the log-transformed values of the best estimated AUC and C_{max} were used for bioequivalence assessment, using the software DAS 3.0. The same procedure was

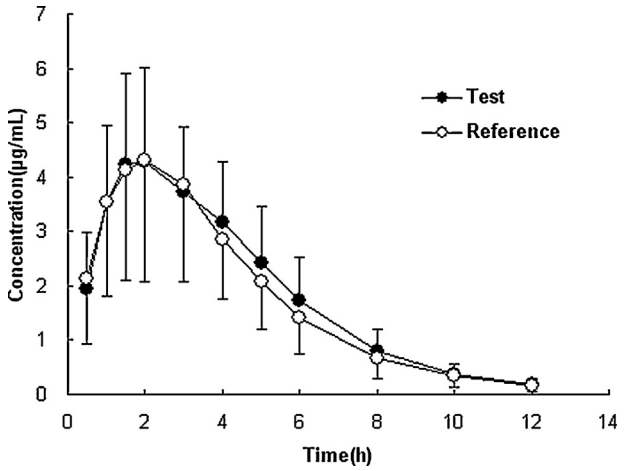

Fig. 1. Mean concentration–time profiles of pidotimod in the serum of healthy Chinese volunteers after single oral doses (800 mg) of the reference and the test formulations. Data are reported as mean ± SD.

applied to the LSS-derived parameters to explore the usefulness of the LSS approach in bioequivalence studies. These two formulations of pidotimod were considered to be equivalent when the AUC and C_{max} values of the test drug were within 80 to 125% of the reference drug values, otherwise the two formulations were considered non-equivalent.

3. Results

3.1. Pharmacokinetics by classical method

All the volunteers completed the study protocol and none experienced clinically relevant adverse effects. The mean serum concentration–time curves for each pidotimod formulation are shown in Fig. 1. The pharmacokinetic parameters are listed in Table 2. The values of C_{max}, AUC_{0-12h}, and $AUC_{0-\infty}$ show no significant differences between the two formulations. The result shows that the 90% confidence intervals (CI_s) for individual percentage ratios of AUC and C_{max} for both test and reference are within the bioequivalence range of 80–125%, which indicates that these two formulations are bioequivalent.

3.2. Multiple regression equation of limited sampling

The concentration data sets from the 20 volunteers enrolled in this study were used to identify the most informative sampling times using one to four samples for estimating the $AUC_{0-12\ h}$ and C_{max}. Three best linear equations were selected according to the coefficient of determination (Table 3). The highest determination coefficient of one sampling point was 0.873 and 0.925 for $AUC_{0-12\ h}$ and C_{max}, respectively. When the sampling points were increased to two points, the highest coefficient of determination were greater than 90%. The mountain plot analysis (Fig. 2) was used to test the agreement agreement between the abbreviated $AUC_{0-12\ h}$ and C_{max} derived from 1-, 2-, 3-, and 4-point approach. The 4-point approach was better than the 1-, 2-, and 3-point approach. However, the two and three point method yields acceptable results.

Table 2
Pharmacokinetic parameters of pidotimod in healthy Chinese volunteers (mean ± SD, $n = 20$).

Parameters	Test	Reference	90 % CI
$AUC_{0-12\ h}$ ($\mu g \cdot min \cdot mL^{-1}$)	22.50 ± 6.88	21.25 ± 8.03	97.3 ~ 118.7
$AUC_{0-\infty}$ ($\mu g \cdot min \cdot mL^{-1}$)	23.04 ± 7.08	21.77 ± 8.15	96.9 ~ 118.7
C_{max} ($\mu g \cdot mL^{-1}$)	4.72 ± 4.72	4.72 ± 2.16	95.1 ~ 109.8

3.3. Model validation

The determination coefficient of the regression equation could be used as a very important measurement for model quality evaluation. However, it cannot reflect the stability of the model. So the internal confirmation was performed by the Jack-knife method. As per the description in objects and methods, one sample is removed each time and the results are listed in Table 4. When using limited sampling 3-points modeling for $AUC_{0-12\ h}$ (5, 2, and 0.5 h) and C_{max} (5, 2, and 1.5 h), in addition to the larger coefficient of determination obtained, RMSE and predicted results error were more than 10%, of which 15% were lowered significantly, which were considered to be the best sampling points. The predicted accuracy was further improved when four points were selected.

In order to intuitively evaluate the accuracy of the prediction, we made a B-A associated diagram of limited sampling [14]. In Figs. 3(a–d) and 4(a–d) are the diagrams of the best assemblies from the possible assemblies selected respectively from the sampling points of 1, 2, 3 and 4. The Y-axis is the percentage error of the observed value minus the predicted value; the central position is the zero error line. The nearer the points are to the line, the better the accuracy is. The dotted line is the 10% predicted error line, while the solid line is the 15% predicted error line. In Figs. 3(a) and 4(a), there are many points outside the 15% predicted error line, indicating that the accuracy evaluation based on one sampling time point is extremely indecisive. From Figs. 3(b) and 4(b), we can see that, the prediction improves significantly when two points are selected, with only a few points outside the 15% predicted error line. The prediction is further improved when taking three points, showing a better linearity. The coefficient of determination is close to 1 ($r^2 = 0.977$ and 0.992). About two to four points blood concentrations of pidotimod can be taken as a predictor to predict the $AUC_{0-12\ h}$ and C_{max}. The $AUC_{0-12\ h}$ can better predict, while all of the above could be selected according to the actual need, in Figs. 3 and 4, an excellent fitting is observed.

Table 3
Coefficient of determination of some of the best linear equations for estimation of $AUC_{0-12\ h}$ and C_{max} in 1–4 sample times strategy.

Parameter	Sampling size	Sampling time (h)	r^2	Linear equation
$AUC_{0-12\ h}$	1	3	0.873	$4.352 + 4.631 \times C_3$
	2	5,2	0.977	$1.625 + 4.661 \times C_5 + 2.274 \times C_2$
	3	5, 2, 0.5	0.989	$0.952 + 4.888 \times C_5 + 1.808 \times C_2 + 1.069 \times C_{0.5}$
	4	5, 2, 1.5, 0.5	0.992	$0.680 + 4.921 \times C_5 + 1.172 \times C_2 + 0.808 \times C_{1.5} + 0.844 \times C_{0.5}$
C_{max}	1	2	0.925	$0.644 + 0.948 \times C_2$
	2	5, 2	0.941	$0.224 + 0.271 \times C_5 + 0.903 \times C_2$
	3	5, 2, 1.5	0.958	$-0.009 + 0.316 \times C_5 + 0.490 \times C_2 + 0.455 \times C_{1.5}$
	4	6, 5, 2, 1.5	0.962	$0.025 - 0.836 \times C_6 + 0.958 \times C_5 + 0.509 \times C_2 + 0.396 \times C_{1.5}$

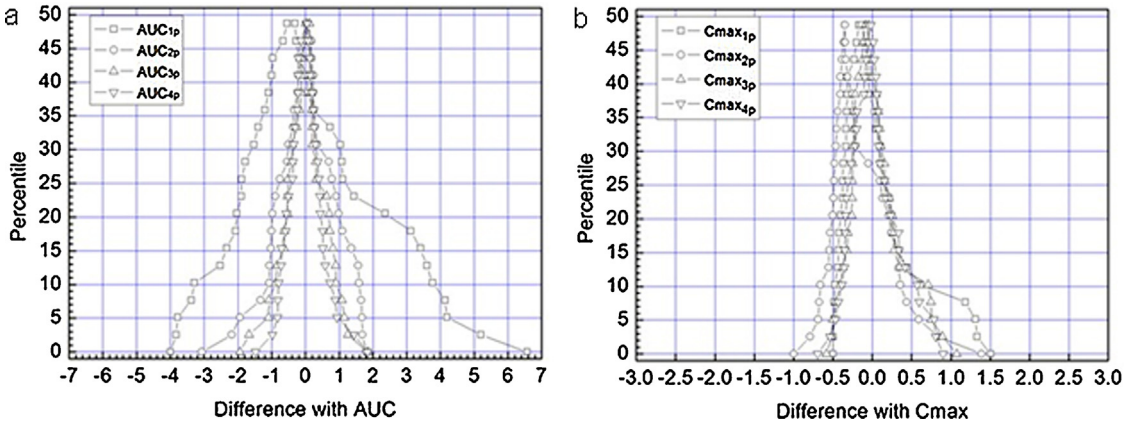

Fig. 2. a: mountain plot analysis testing agreement between the abbreviated $AUC_{0-12\ h}$ derived from C_3, C_5C_2, $C_5C_2C_{0.5}$, and $C_5C_2C_{1.5}C_{0.5}$; b: mountain plot analysis testing agreement between the abbreviated C_{max} derived from C_2, C_5C_2, $C_5C_2C_{1.5}$, and $C_6C_5C_2C_{1.5}$. The 4-point approach was better than the 1-, 2-, and 3-point approach; however, the 3-point method yields acceptable result.

3.4. Bioequivalence analysis

The accuracy of the 1–4 point LSS models as predictors of $AUC_{0-12\ h}$ and C_{max} led us to explore their potential usefulness in assessing the bioequivalence of the pidotimod formulations studied. Table 5 contains the pharmacokinetic parameters mean estimates, and their respective confidence intervals. The 90% CI's of the individual percent ratios (test/reference formulation) of the in-transformed $AUC_{0-12\ h}$ and C_{max} of pidotimod, calculated by classic method or the LSS-derived metrics, were very in close and were within the accepted bioequivalence range of 80 to 125%. Analysis of variance (Anova) showed no statistically significant ($P > 0.05$) difference between test and reference products. This is interpreted as indicating that the two pidotimod formulations are bioequivalent.

4. Discussion

A limited sampling strategy (LSS) is a new collected samples method used by investigators to estimate drug pharmacokinetics and to monitor drug-dosing schedules [16]. In recent years, LSS has been used to monitor drug dosing in the clinic [17]. LSS methods use blood concentrations measured at less sampling points to established mathematical models and have been validated to provide accurate estimations of pharmacokinetic parameters [18]. In the present study, we explored the usefulness of LSS models for estimating pharmacokinetic parameters and assessing the bioequivalence of pidotimod following oral administration of the drug to healthy individuals. The application of LSS models to bioequivalence studies can reduces the cost and cycle time [19,20].

These strategies were developed using data from a bioequivalence study in which a relatively large number of plasma samples ($n = 440$) were collected from closely monitored and healthy Chinese volunteers. In this study a multiple regression model is applied to obtain the order, based on the determination coefficient with the help of computer programming to calculate all the possible assemblies from 1 to 4 points. A large amount of sampling data is used in this case and the regression model is very reliable, with considerable values of reference for other cases with similar samples. This method is relatively more convenient compared with the trapezoidal method. Our LSS analysis and validation procedures indicate that the plasma $AUC_{0-12\ h}$ and C_{max} of pidotimod following oral administration of a single 800 mg dose can be predicted accurately using only two to three plasma samples. The highest determination coefficients of two sampling points were 0.977 and 0.941 for $AUC_{0-12\ h}$ and C_{max} and the best sampling time points were at (5,2 h). Choosing three or more samples adds little to the accuracy and precision of the estimates. The present study indicates that the implementation of an 800 mg dosage regimen enabled accurate predictions of $AUC_{0-12\ h}$ and C_{max} by the LSS model. The modeling of pidotimod in this case is validated internally by the Jack-knife method. The high rate of accuracy of the limited sampling model of pidotimod is thus proven, and 2–4 points could be selected for the prediction in accordance with actual needs.

The traditional method of analysis has been frequently used in the past for bioequivalence evaluation. But several reports in the literature have suggested the usefulness of the LSS model analysis for bioequivalence evaluation [19–21]. In the present study, bioequivalence was assessed using both the traditional method

Table 4
Jack-knife validation of APE and RMSE in the different sampling strategies for prediction of $AUC_{0-12\ h}$ and C_{max}.

	Sampling size	Sample time (h)	r^2	RMSE	L_{APE}[a]	U_{APE}[b]	>10%[c]	>15%[d]
$AUC_{0-12\ h}$	1	3	0.873	23.175	0.640	44.348	18	9
	2	5, 2	0.977	10.035	0.435	22.542	2	2
	3	5, 2, 0.5	0.989	6.034	0.063	12.012	1	0
	4	5, 2, 1.5, 0.5	0.992	4.555	0.180	10.771	0	0
C_{max}	1	2	0.925	23.175	0.640	44.348	16	8
	2	5, 2	0.941	6.421	0.198	18.369	19	9
	3	5, 2, 1.5	0.958	6.034	0.063	12.012	12	3
	4	6, 5, 2, 1.5	0.962	4.555	0.180	10.771	12	3

[a] The lower limited prediction error.
[b] The upper limited prediction error.
[c] Number and ratio of calculated $AUC_{0-12\ h}$ with a prediction error beyond 10%.
[d] Number and ratio of calculated $AUC_{0-12\ h}$ with a prediction error beyond 15%.

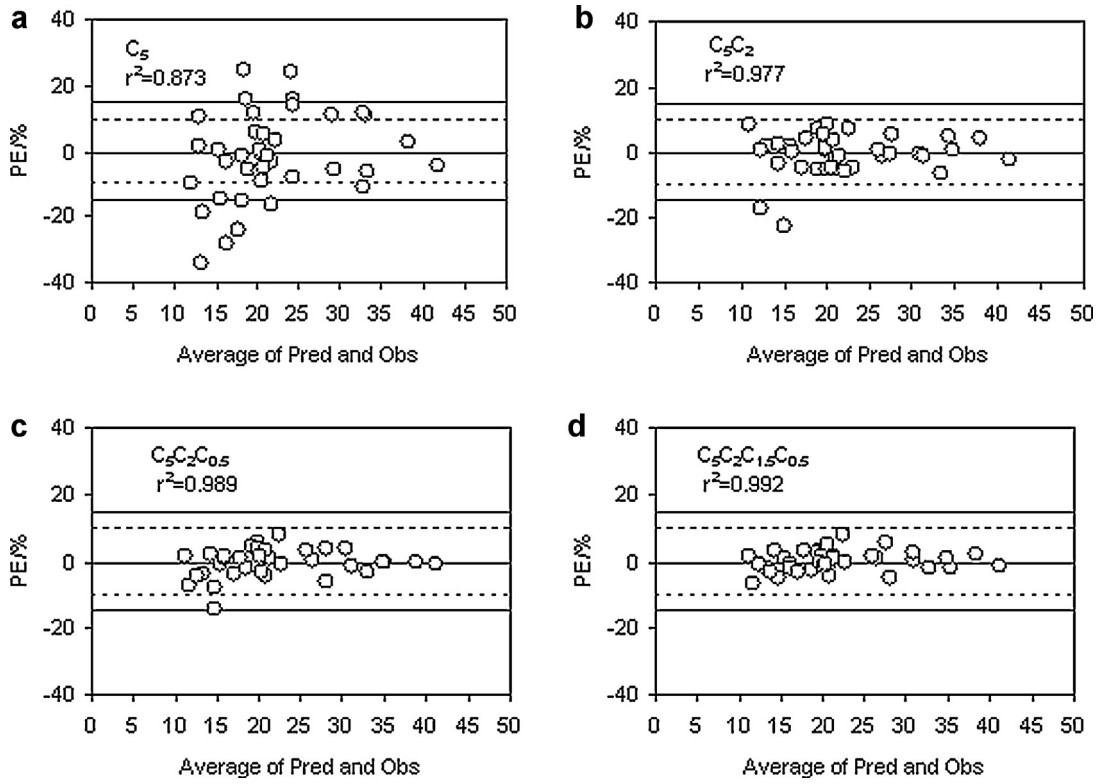

Fig. 3. B-A plots of $AUC_{0-12\ h}$ predicted by each LSS: a: 1-sample LSS; b: 2-sample LSS; c: 3-sample LSS; d: 4-sample LSS.

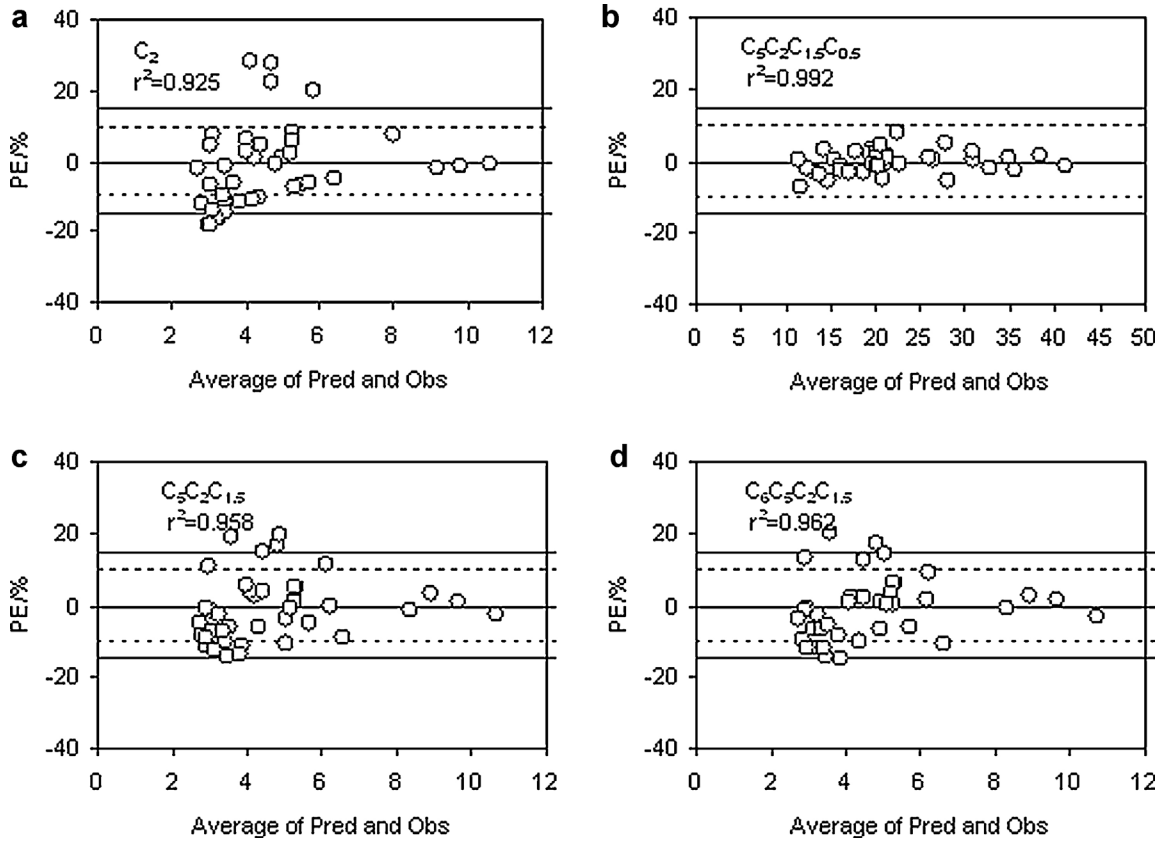

Fig. 4. B-A plots of C_{max} predicted by each LSS: a: 1-sample LSS; b: 2-sample LSS; c: 3-sample LSS; d: 4-sample LSS.

Table 5
Bioequivalence assessment of the original data and the limited sampling strategy-derived data.

Parameters	Test	Reference	90 % CI
$AUC_{0-12\,h}$ ($\mu g \cdot min \cdot mL^{-1}$)			
Classic observed value	22.50 ± 6.88	21.25 ± 8.03	97.3 ~ 118.7
LSS-1 point predictive values	21.55 ± 5.58	22.20 ± 8.18	91.1 ~ 109.2
LSS-2 point predictive values	22.67 ± 6.85	21.09 ± 7.85	98.8 ~ 120.2
LSS-3 point predictive values	22.61 ± 7.01	21.15 ± 7.82	97.9 ~ 119.1
LSS-4 point predictive values	22.67 ± 6.96	21.08 ± 7.87	99.0 ~ 119.8
C_{max} ($\mu g \cdot mL^{-1}$)			
Classic observed value	4.72 ± 4.72	4.72 ± 2.16	95.1 ~ 109.8
LSS-1 point predictive values	4.71 ± 1.65	4.72 ± 2.10	93.2 ~ 111.8
LSS-2 point predictive values	4.96 ± 1.71	4.88 ± 2.22	95.0 ~ 114.3
LSS-3 point predictive values	4.79 ± 1.67	4.64 ± 2.14	97.7 ~ 114.7
LSS-4 point predictive values	4.77 ± 1.66	4.67 ± 2.16	97.2 ~ 113.7

and the LSS model. The complete pharmacokinetic profile of pidotimod associated with the administration of the two formulations was described in the healthy volunteers. The results of this study indicate that a generic formulation of pidotimod is bioequivalent with the reference product. And the results of LSS method and traditional method are very closely similar.

In conclusion, a LSS method was developed and can be used to predict the pharmacokinetic parameters and assess the bioequivalence of pidotimod with less sampling points, and the methodology presented here may also be applicable to bioequivalence evaluation of other medications.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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References

[1] Burgio GR, Marseglia GL, Severi F, De Benedetti F, Masarone M, Ottolenghi A, et al. Immunoactivation by pidotimod in children with recurrent respiratory infections. Arzneimittelforschung 1994;44(12A):1525–9.
[2] D'Angelo L, De Ponti F, Crema F, Caravaggi M, Crema A. Effect of food on the bioavailability of pidotimod in healthy volunteers. Arzneimittelforschung 1994;44(12A):1473–5.
[3] Dickinson L, Back D, Pozniak A, et al. Limited-sampling strategy for the prediction of boosted hard-gel saquinavir exposure at a dosage of 1000/100 mg twice daily in human immunodeficiency virus-infected individuals. Ther Drug Monit 2007;29:361–7.
[4] Spotti D, Biffi M, Coppi G, Silingardi S, Mailland F. Pharmacokinetics of pidotimod in elderly volunteers and in renal failure patients. Arzneimittelforschung 1994;44(12A):1470–2.
[5] Johnston A, Sketris I, Marsden JT, et al. A limited sampling strategy for the measurement of cyclosporine AUC. Transplant Proc 1990;22:1345–6.
[6] Monchaud C, Rousseau A, Leger F, et al. Limited sampling strategies using Bayesian estimation or multilinear regression for cyclosporin AUC(0-12) monitoring in cardiac transplant recipients over the first year post-transplantation. Eur J Clin Pharmacol 2003;58:813–20.
[7] Zicheng Y, Peijun Z, Da X, et al. Investigation on pharmacokinetics of mycophenolic acid in Chinese adult renal transplant patients. Br J Clin Pharmacol 2006;62:446–52.
[8] Bolon-Larger M, Chamouard V, Bressolle F, et al. A limited sampling strategy for estimating individual pharmacokinetic parameters of coagulation factor VIII in patients with hemophilia A. Ther Drug Monit 2007;29:20–6.
[9] Huang JH, Wang K, Huang XH, He YC, Li LJ, Sheng YC, et al. Limited sampling strategy models for estimating the AUC of gliclazide in Chinese healthy volunteers. Eur J Drug Metab Pharmacokinet 2012 [Epub ahead of print].
[10] Huang XH, Huang JH, Wang Qin, Wang K. Calculating the pharmacokientic parameters of cefaclor in healthy volunteers using limited sampling model. Chin J Clin Pharm Ther 2012;17(4):421–7.
[11] Lou HG, Ruan ZR, Jiang B. Quantitative determination of pidotimod in human plasma by liquid chromatography tandem mass spectrometry: application to a bioequivalence study. Arzneimittelforschung 2012;62(2):99–104.
[12] Quenouille M. Approximate tests of correlation in time series. J R Stat Soc Series B Stat Methodol Series B 1949;11.
[13] Quenouille M. Notes on bias in estimation. Biometrika 1956;61.
[14] Dupuis LL, Sibbald C, Schechter T, et al. IV busulfan dose individualization in children undergoing hematopoietic stem cell transplant: limited sampling strategies. Biol Blood Marrow Transplant 2008;14:576–82.
[15] Filler G. Abbreviated mycophenolic acid AUC from C0, C1, C2, and C4 is preferable in children after renal transplantation on mycophenolate mofetil and tacrolimus therapy. Transpl Int 2004;17(3):120–5.
[16] Chen LF, Jiao JJ, Zhang CL, Lou JS, Liu CX. Bioequivalence assessment of metformin hydrochloride using a limited sampling strategy. Int J Clin Pharmacol Ther 2011;49(10):629–36.
[17] N'Dri-Stempfer B, Navidi WC, Guy RH, Bunge AL. Improved bioequivalence assessment of topical dermatological drug products using dermatopharmacokinetics. Pharm Res 2009;26(2):316–28.
[18] Suarez-Kurtz G, Estrela Rde C, Salvadori MC. Prednisolone: limited sampling strategies for estimating pharmacokinetic parameters. Ther Drug Monit 2004;26(1):16–22.
[19] Suarez-Kurtz G, Ribeiro FM, Salvadori MC, Struchiner CJ, Carbamazepine:. a bioequivalence study and limited sampling modeling. Int J Clin Pharmacol Ther 2002;40(9):424–30.
[20] Mahmood I, Mahayni HA. limited sampling approach in bioequivalence studies: application to long half-life drugs and replicate design studies. Int J Clin Pharmacol Ther 1999;37(6):275–81.
[21] Mahmood I, Chamberlin N, Tammara V. A limited sampling approach in bioequivalence studies. Ther Drug Monit 1997;19(4):413–9.