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Research Article

Assessment of Bioequivalence of Two Tramadol Hydrochloride 100 mg Extended-Release Tablet Formulations in Healthy Thai Volunteers

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ABSTRACT

Tramadol hydrochloride 100 mg extended-release tablets is available as the registered trademark, Tramal® retard in Thailand to reduce a dosing frequency for the treatment of moderate to severe pain. The Government Pharmaceutical Organization had developed the generic tramadol hydrochloride 100 mg extended-release tablets (Tramadol retard GPO®) to serve as an alternative product which is more accessible and affordable without compromising quality. Two separate single-dose bioequivalence studies under fasting and fed conditions and one multiple-dose bioequivalence study under fasting conditions were conducted in healthy Thai volunteers using a comparative randomized, two-way crossover, open-label design to demonstrate the equivalence in biopharmaceutics quality between two tramadol formulations. Tramadol plasma concentrations were quantified using a validated liquid chromatography-mass spectrometry method. The 90% confidence intervals for the geometric least squares mean ratios of log-transformed $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max} for the single-dose studies and log-transformed $AUC_{0\text{-}\tau,ss}$, $C_{\tau,ss}$ and $C_{max,ss}$ for the multiple-dose study were within 80.00%-125.00% of bioequivalence criteria. The analysis of variance did not show significant effect of the formulation on the primary pharmacokinetic parameters. Wilcoxon signed-rank test also showed no significant difference in median t_{max} between two formulations in any studies. Bioequivalence between the test and reference products was concluded based on insignificant difference in terms of rate and extent of absorption.

Keywords: Tramadol; Bioequivalence; Pharmacokinetics; Extended-Release

INTRODUCTION

Tramadol is a synthetic opioid exerting the analgesic properties by binding to mu-opioid receptors with high affinity, as well as weakly inhibiting serotonin and norepinephrine reuptake. Tramadol is converted to O-desmethyltramadol which also contributes to analgesic activity by Cytochrome P450 (CYP) 2D6 [1]. It is indicated for the management of moderate to severe pain in adults as single or in combination with other analgesics. Unlike other opioid analgesics, tramadol has more favorable safety profile and low abuse rates have been demonstrated [2]. As tramadol is available in various pharmaceutical formulations for oral, sublingual, intranasal, rectal, intravenous, subcutaneous, and intramuscular administration, the selection of appropriate formulation is essential for the attainment of treatment goals [3].

For oral dosage forms, the recommended dose of immediate-release formulations of tramadol is 50-100 mg every 4 to 6 hours. However, dosing frequency and peak-trough fluctuation of immediate-release formulations are highly associated with pain management and adverse events. Several extended-release formulations have demonstrated the reduced maximum plasma concentration compared with the immediate-release formulation, thereby minimizing the occurrence of concentration-dependent adverse events. In addition, the dosing frequency of extended-release formulations can be reduced to once or twice daily, and thus enhance patient adherence to medication [4–6]. Tramadol hydrochloride 100 mg extended-release tablets are available as the registered trademark, Tramal® retard in Thailand. The usual initial dose in adults is 100 mg twice daily and it can be increased to the maximum daily dose of 400 mg [7]. The absolute bioavailability of the extended-release tablets is 67.3% which is comparable with the immediate-release tablets. However, the bioavailability is 87.4% relative to immediate-release capsules at steady state. The extended-release tablets can be administered with or without food as food intake dose not significantly influence the absorption rate [1].

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The Government Pharmaceutical Organization (GPO), Thailand had developed the generic tramadol hydrochloride 100 mg extended-release tablets (Tramadol retard GPO®) to serve as an alternative product which is more accessible and affordable without compromising quality. Bioequivalence of oral modified-release formulations should be demonstrated in fasting and fed conditions to evaluate the effect of food on the bioavailability. It is also required to assess the bioequivalence at steady state if high extent of accumulation is expected [8]. Therefore, two separate single-dose bioequivalence studies under fasting and fed conditions and one multiple-dose bioequivalence study under fasting conditions were conducted to demonstrate the equivalence in biopharmaceutics quality between two tramadol formulations.

MATERIALS AND METHODS

Study products

Tramadol retard GPO® (Tramadol hydrochloride 100 mg extended-release tablets), manufactured by The Government Pharmaceutical Organization (GPO), Thailand was used as the test product. Tramal® retard 100 mg (Tramadol hydrochloride 100 mg prolonged-release tablets), manufactured by Grunenthal GmbH, Germany was used as the reference product.

Study subject

Sample size was calculated based on the power of greater than 90% for concluding bioequivalence within the acceptance bioequivalence limits of 80.00%-125.00% at a significant level of 5% [9]. The reported intra-subject variability for maximum concentration (C_{max}) of tramadol was around 12% and the expected T/R ratio was 90% for the single-dose fasting study which yielded a sample size of 19 subjects [10]. However, 24 subjects were enrolled considering 20% dropouts. By assuming similar intra-subject variability on the primary pharmacokinetics parameters as observed in the single-dose fasting study, 10.5% CV of C_{max} was used for sample size calculation in the single-dose fed study. Therefore, 14 subjects were enrolled in the single-dose fed study. Higher intra-subject variability was anticipated for the multiple-dose study, and thus intra-subjects variability of 18% was assumed [11]. Therefore, 58 subjects were enrolled in the multiple-dose fasting study by including 30% dropouts.

The enrolled subjects were healthy males and females at the age between 18 and 55 years, having Body Mass Index (BMI) between 18.0 and 30.0 kg/m^2. They had no evidence of underlying disease or abnormal findings from physical and laboratory examinations. They had no history of drug allergy, especially to the study drug. They did not participate in other clinical trials or donate at least 1 unit of blood within 90 days prior to the start of each study. They were screened for alcohol consumption and recreational drug use. A negative pregnancy test and non-breastfeeding were additionally required for female subjects. Prior to dosing and during the trials, the subjects were instructed to abstain from tobacco smoking and taking medications including over-the-counter products and herbal remedies. Consumption of any grapefruit, pomelo or orange-based products, and xanthine containing products were restricted at least 24-48 hours prior to dosing and throughout the study.

Study design

Three separate, open-label, randomized, two-treatment, two-period, two-sequence, crossover studies were conducted under single-dose fasting (S1), single-dose fed (S2) and multiple-dose fasting (S3) conditions. In the single-dose fasting study, each subject randomly received an assigned formulation after 10-hour overnight fasting. In contrast, the product was administered at 30 minutes after having high fat and high calories breakfast in the single-dose fed study. Seven days wash-out period was given between period I and period II of the single-dose studies. There were total 23 and 24 blood samples collected up to 48 hours post-dose in each period of the single-dose fasting and fed studies, respectively.

The multiple-dosing study was conducted under fasting conditions. In each period, total 9 doses of the study product were administered at a dosing interval of 12 hours. The morning doses were administered after at least 8 hours overnight fasting whereas the evening doses were administered after at least 2 hours fasting. Wash-out period of 10 days was applied between last dose of period I and first dose of period II. Four pre-dose samples were collected before the morning dose on day 1, 3, 4 and 5. Total 16 post-dose samples were collected for 12 hours after last dose administration on day 5.

The bioequivalence studies were conducted as per the protocol, ICH 'Guidance on Good Clinical Practice' and Declaration of Helsinki. The clinical study protocols were approved by the Institute for the Development of Human Research Protection (IHRP), Department of Medical Sciences, Ministry of Public Health, and Thailand. The subjects were informed about risks and benefits of the studies and gave written informed consent before study participation.

Sample analysis

Blood samples were collected in vacutainers containing sodium heparin as an anticoagulant, and were centrifuged at 3000 relative centrifugal force (rcf) and 4°C for 5 minutes to separate plasma. Plasma samples were stored in freezer at -55°C or colder until completion of analysis. The plasma samples were processed and analyzed using in-house method validated as per EMA guideline on bioanalytical method validation and US FDA bioanalytical method validation guidance for industry [12,13]. Tramadol and tramadol-d6 were extracted from 250 µL of plasma using liquid-liquid extraction technique. Briefly, 0.1 M sodium hydroxide and diethyl ether were added to each sample. Then, the samples were centrifuged at 3400 rcf and 10°C for 5 minutes, and subsequently flash frozen to separate the organic layer. The organic layer was evaporated at 40°C to dryness and reconstituted with 5 mM ammonium acetate buffer (pH 4.5) : methanol (30:70, v/v).

Plasma concentration of tramadol was determined by liquid chromatography-tandem mass spectrometer (LC-MS/MS): Nexera™ (Shimadzu Corporation, Japan) coupled with TSQ Quantum Ultra (Thermo Fisher Scientific, USA). The samples were injected at 5 µL onto ACE 5 C18, 150 × 4.6 mm column. The temperature of column oven was set at 40°C. The isocratic mobile phase consisting of 5 mM ammonium acetate buffer (pH 4.5) : methanol (30:70, v/v) was pumped at a flow rate of 0.7 mL/minute. The transition of precursor to product ion was monitored in positive mode at m/z 264.200 to 58.130 for tramadol, and m/z 270.231 to 64.150 for tramadol-d6. The calibration curve range was 2.000-800.789 ng/mL. Data acquisition and evaluation of chromatographic data were performed using Xcalibur™ version 3.0.63.3 and LCquan™ version 2.9.0.34 (Thermo Fisher Scientific Inc., USA).

Pharmacokinetic and statistical analysis

In the single-dose studies, the pharmacokinetic parameters were calculated by non-compartmental analysis using Phoenix® WinNonlin® Software Version 6.3 (Pharsight Corporation, USA)

and the statistical analysis was carried out using PROC GLM of SAS® Version 9.3 (SAS Institute Inc., USA). The area under the curve from time zero to last observed concentration ($AUC_{0\text{-tlast}}$), the area under the curve from time zero to infinity ($AUC_{0\text{-}\infty}$) and the C_{max} were primary pharmacokinetic parameters. The time to reach C_{max} (t_{max}), the elimination half-life ($t_{1/2}$) and the elimination rate constant (λ_z) were secondary pharmacokinetic parameters.

In the multiple-dose study, the pharmacokinetic parameters were calculated using non-compartmental model (Phoenix® WinNonlin® software Version 6.4, Pharsight Corporation, USA). The area under the curve during dosing interval at steady state ($AUC_{0\text{-}\tau,ss}$), the plasma concentration at the end of dosing interval at steady state ($C_{\tau,ss}$) and the maximum plasma concentration at steady state ($C_{max,ss}$) were primary pharmacokinetic parameters. The time at maximum plasma concentration during dosing interval at steady state ($t_{max,ss}$), the plasma concentration prior to dosing (C_{pd}), the average plasma concentration at steady state ($C_{av,ss}$) and the peak-trough fluctuation over dosing interval at steady state (%Fluctuation) were secondary pharmacokinetic parameters. The statistical analysis was performed using PROC MIXED (SAS® Version 9.4, SAS Institute Inc., and USA).

Analysis of Variance (ANOVA) was performed for log-transformed primary pharmacokinetic parameters. ANOVA model included period, formulation and sequence as fixed effects and subject (sequence) as a random effect. Sequence effect was tested using subject (sequence) as an error term. The significance of these effects was determined using F-test. The bioequivalence assessment was determined upon 90% Confidence Interval (CI) for the ratio of geometric least squares mean of the primary pharmacokinetic parameters. Bioequivalence of two formulations was to be concluded if the 90% CIs fell within acceptance range of 80%.00-125.00%. Wilcoxon signed-rank test was performed to compare median t_{max} and $t_{max,ss}$ of the test and reference products. Repeated measure ANOVA was performed on log-transformed C_{pd} (last three morning pre-dose concentrations on day 3 to day 5) to confirm the attainment of the steady state in the multiple-dose study. All statistical calculations were performed at a significance level of 5% (α=0.05).

RESULTS

Demographic characteristics of subjects

In the single-dose fasting study, twenty-four healthy Thai male and female subjects were enrolled. The mean ± SD of age and BMI of enrolled subjects were 28.17 ± 7.73 years and 22.21 ± 1.90 kg/m^2, respectively. There were two subjects withdrawn due to emesis within 12 hours after dosing and one subject dropped out before initiation of period II due to personal reason. In the single-dose fed study, there were fourteen subjects enrolled in the study but there were two subjects withdrawn due to emesis within 12 hours after dosing in period I. The mean ± SD of age and BMI of enrolled subjects were 36.71 ± 9.38 years and 22.12 ± 1.84 kg/m^2, respectively. In the multiple-dose study, total fifty-eight subjects were enrolled but forty-seven subjects completed the study. There were five subjects withdrawn in period I while two subjects were withdrawn in period II due to emesis within 12 hours after dosing. One subject was withdrawn in period II upon receiving antiemetic drug for alleviating nausea. Additional 3 subjects dropped out before initiation of period II due to personal reason. The mean ± SD of age and BMI of enrolled subjects were 34.19 ± 8.95 years and 23.06 ± 2.75 kg/m^2, respectively.

Pharmacokinetic and statistical analysis

The pharmacokinetic data from twenty-one subjects who completed the single-dose fasting study were summarized in Table 1. The mean $AUC_{0\text{-tlast}}$ was 3567.6 ng.hr/mL and 3655.3 ng.hr/mL for the test and reference formulations, respectively. After oral administration of both products under fasting conditions, the mean C_{max} around 250 ng/mL was attained at the median t_{max} of 4.5 hours. The mean $t_{1/2}$ was approximately 7 hours for both formulations. In contrast, the pharmacokinetic data of the test and reference formulations following single dose administration under fed conditions were computed from 12 subjects. The mean $AUC_{0\text{-tlast}}$ values were slightly lower than those observed in the single-dose fasting study. However, the mean C_{max} of both formulations was increased to around 270 ng/mL. Generally, the pharmacokinetic parameters of tramadol administered under fasting and fed states were comparable. The mean plasma concentration-time profiles of tramadol after single dose administration of the test and reference products under fasting and fed conditions are illustrated in Figure 1A and 1B, respectively.

Upon multiple dosing, the C_{pd} values observed on day 3 to 5 were not significantly different (repeated measure ANOVA, p-value=0.8973) indicating that the steady state had been achieved. The mean $AUC_{0\text{-}\tau,ss}$ calculated after last dose administration of the test and reference products was 4537.3 and 4555.5 ng.hr/mL, respectively. The mean $C_{\tau,ss}$ measured at 12 hour after last dose administration was 270.4 and 275.7 ng/mL for the test and reference formulations, respectively. The $C_{max,ss}$ was remarkably higher than the C_{max} observed in the single-dose studies; however, the t_{max} and $t_{1/2}$ were not significantly different between single dose and multiple dose administration. The mean peak-trough fluctuation for tramadol was 56.1% for the test product and 51.4% for the reference product. The mean plasma concentration-time profiles of tramadol after 9th dose administration of the test and reference products for 12 hours are illustrated in Figure 1C and the pharmacokinetic parameters are summarized in Table 2.

The ANOVA indicated no significant effects of sequence, formulation and period on the log-transformed primary pharmacokinetic parameters (p-value>0.05) (Table 3). In addition, the 90% CIs of the geometric least squares mean ratio between the formulations for log-transformed primary pharmacokinetic parameters were within the acceptance range for bioequivalence. Wilcoxon signed-rank test did not detect the significant difference in the median t_{max} between the test and reference formulations in any studies (p-value>0.05).

Tolerability

Based on the safety evaluation in three studies, both test and reference products were well tolerated by the study subjects. Total 11 adverse events were reported in 4 subjects in the single-dose fasting study while 23 adverse events were reported in 9 subjects in the single-dose fed study. The highest incidence was observed in the multiple-dose study, in which 80 adverse events were reported in 43 subjects. All adverse events were mild to moderate in the severity. The list of adverse events after receiving the test and reference products are shown in Table 4. The most common adverse events were dizziness, nausea, vomiting and pruritis which were probably related to the study drug. All subjects who had adverse events were closely monitored and received supportive treatment until they recovered.

Table 1: Pharmacokinetic parameters of tramadol for the test and reference products following single dose administration.

Parameter (Unit)	Single-dose fasting; S1 (Mean ± SD, N=21)		Single-dose fed; S2 (Mean ± SD, N=12)	
	Test	Reference	Test	Reference
$AUC_{0\text{-tlast}}$ (ng.hr/mL)	3567.6 ± 1023.5	3655.3 ± 1110.8	3339.1 ± 1124.8	3392.4 ± 1091.6
$AUC_{0\text{-}\infty}$ (ng.hr/mL)	3632.8 ± 1059.4	3725.7 ± 1146.4	3398.6 ± 1164.6	3459.8 ± 1138.7
C_{max} (ng/mL)	255.4 ± 64.7	249.2 ± 63.4	271.3 ± 61.3	274.6 ± 55.3
t_{max} (hr, in median (min, max))	4.5 (2.5, 5)	4.5 (2.5, 7)	4.5 (3.5, 8)	4.25 (2.5, 5.5)
λ_Z (1/hr)	0.10 ± 0.02	0.10 ± 0.02	0.11 ± 0.03	0.11 ± 0.03
$t_{1/2}$ (hr)	7.13 ± 1.15	7.28 ± 1.25	6.79 ± 1.86	7.03 ± 1.86
% AUC extrapolation	1.70 ± 0.69	1.79 ± 0.86	1.62 ± 0.62	1.78 ± 0.88

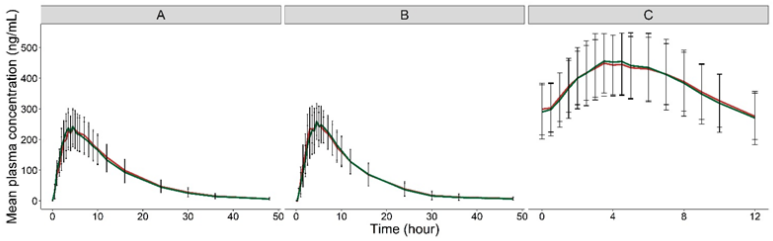

Figure 1: Mean plasma concentration-time profiles of tramadol after administration of test product-T and reference product-R in single-dose fasting study (A), single-dose fed study (B), and multiple-dose fasting study (C). **Note:** (—) Reference; (—) Test.

Table 2: Pharmacokinetic parameters of tramadol for the test and reference products following multiple dose administration.

Parameter (Unit)	Multiple-dose fasting; S3 (Mean ± SD, N=45)	
	Test	Reference
$C_{max,ss}$ (ng/mL)	471.8 ± 112.5	462.6 ± 100.6
$C_{\tau,ss}$ (ng/mL)	270.4 ± 86.9	275.7 ± 75.6
$AUC_{0\text{-}\tau,ss}$ (ng.hr/mL)	4537.3 ± 1195.6	4555.5 ± 1060.4
C_{pd} (ng/mL)		
Day 1	0.0 ± 0.0	0.3 ± 1.7
Day 3	277.6 ± 93.6	282.1 ± 81.8
Day 4	280.5 ± 91.4	288.9 ± 87.7
Day 5	290.1 ± 88.5	299.4 ± 84.3
t_{max},ss (hr, in median (min,max))	4.5 (2.5,7)	4 (2.5,7)
$C_{av,ss}$ (ng/mL)	378.1 ± 99.6	379.6 ± 88.4
$t_{1/2}$ (hr)	7.13 ± 1.15	7.28 ± 1.25
% Fluctuation	56.1 ± 11.8	51.4 ± 10.8

Table 3: Statistical comparison of primary pharmacokinetic parameters between the test and reference products.

Parameter	Geometric least squares mean ratio (90% CI)	Power	Intra subject CV (%)	ANOVA (p-value)		
				Sequence	Formulation	Period
Single-dose fasting (N=21)						
ln $AUC_{0\text{-tlast}}$	97.9 (95.08-100.84)	100	5.5	0.819	0.2313	0.5167
ln $AUC_{0\text{-}\infty}$	97.8 (95.04-100.68)	100	5.4	0.8016	0.2013	0.4603

ln C_{max}	102.3 (96.71-108.17)	100	10.5	0.986	0.4954	0.087
Single-dose fed (N=12)						
ln $AUC_{0\text{-}tlast}$	98.0 (92.86-103.42)	100	7.2	0.9152	0.5117	0.5046
ln $AUC_{0\text{-}\infty}$	97.9 (92.64-103.40)	100	7.3	0.8875	0.495	0.4641
ln C_{max}	98.0 (93.25-102.93)	100	6.6	0.9398	0.4691	0.4649
Multiple-dose fasting (N=45)						
ln $C_{max,ss}$	101.8 (98.86-104.78)	100	8.1	0.5796	0.3154	0.1529
ln $C_{\tau,ss}$	96.9 (92.96-100.95)	100	11.5	0.484	0.2017	0.1445
ln $AUC_{0\text{-}\tau,ss}$	99.0 (96.13-102.05)	100	8.4	0.554	0.5924	0.0893

Table 4: List of adverse events.

Adverse event	Incidence (N)					
	Test			Reference		
	S1	S2	S3	S1	S2	S3
Dizziness	1	3	11	1	4	6
Nausea	2	2	8	0	2	7
Vomiting	2	0	4	0	2	3
Increased sweating	1	0	0	1	1	0
Loss of appetite	0	1	0	0	0	0
Difficulty swallowing of saliva	0	1	0	0	0	0
Dry mouth	1	0	0	0	1	1
Thirsty	0	0	0	0	1	0
Fever	0	1	0	0	0	0
Somnolence	1	0	0	0	0	0
Faintness	0	0	0	1	0	1
Headache	0	0	0	0	0	1
Numbness	0	0	2	0	0	1
Abdominal discomfort	0	2	0	0	1	0
Diarrhea/loose stool	0	1	1	0	0	0
Constipation	0	0	1	0	0	0
Dyspepsia	0	0	1	0	0	0
Flatulence	0	0	0	0	0	1
Palpitation	0	0	2	0	0	0
Asymptomatic hypotension	0	0	1	0	0	0
Blurred vision	0	0	1	0	0	0
Increased ALT/AST	0	0	1	0	0	3
Increased creatinine	0	0	1	0	0	2
Increased blood glucose	0	0	4	0	0	4
Increased total bilirubin	0	0	0	0	0	2
Pruritis	0	0	4	0	0	6
Total	8	11	42	3	12	38

DISCUSSION

The bioequivalence between the test and reference formulations was evaluated following single dose administration under fasting and fed conditions. The pharmacokinetics parameters observed in both studies were comparable between the test and reference formulations. In addition, the pharmacokinetics of tramadol was not significantly difference when the products were administered under fasting and fed conditions. However, the mean C_{max} was slightly increased in the single-dose fed study compared with that in the single-dose fasting study which was in accordance with the data previously reported for the extended-release formulation of tramadol [1]. The data from the single-dose studies suggested high extent of accumulation of tramadol since the $AUC_{0-\tau}$ was less than 90% of the $AUC_{0-\infty}$, thus demonstration bioequivalence at steady-state is required.

The multiple-dose study was conducted under fasting conditions as it is more sensitive to detect the difference between the formulations that can be taken with or without food [14]. The longer washout period was applied in the multiple-dose study to ensure complete drug elimination; however, the data from two complete subjects were excluded from the bioequivalence calculation due to concentration greater than 5% of C_{max} observed in pre-dose samples of period II as per EMA guideline on the investigation of bioequivalence. Therefore, the data of 45 subjects were eligible for bioequivalence evaluation at steady-state. According to the data, the steady-state was achieved as early as on day 3. The $C_{max,ss}$ was almost double than the C_{max} observed in the single-dose studies suggesting the accumulation of tramadol after repeated dosing.

Although there is an active metabolite which has higher analgesic potency than the parent compound [15], the bioequivalence of two tramadol hydrochloride 100 mg extended-release tablet formulations was concluded solely based on the pharmacokinetics of tramadol for the reason that the rate and extent of absorption derived from parent compound is more relevant to drug release from the formulation [14]. In all studies, the bioequivalence between the test and reference formulations was successfully demonstrated with the power greater than 90%. Most adverse events reported in the present studies had been previously reported for tramadol and other opioids [3,16,17]. The greater incidence of adverse events was observed in the multiple dose study which might be due to higher drug exposure in this study. However, the tolerability after chronic use should be further investigated.

CONCLUSION

The test product, Tramadol retard GPO® and reference product, Tramal® retard 100 mg were bioequivalent as evident from the single-dose and multiple-dose studies. The 90% CIs of the geometric least squares mean ratio between the formulations for log-transformed primary pharmacokinetic parameters were within the acceptance range of 80.00%–125.00% in all three studies. Both treatments were well tolerated and no serious adverse event was found.

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