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Research paper

# Influence of food on the oral bioavailability of deramciclane from film-coated tablet in healthy male volunteers

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**Abstract**

The effect of a high-fat meal on the oral bioavailability of deramciclane 30 mg tablet was evaluated in 18 healthy male volunteers in a randomised, single dose, two-way crossover study. The drug was administered following an overnight fast or a standardised high-fat breakfast. The plasma concentrations of deramciclane and *N*-desmethylderamciclane were determined by using a validated HPLC–MS–MS/MS method. An effect of food on the bioavailability was indicated if the 90% confidence interval (CI) for the ratio of geometric means of fed and fasted treatments was not contained in the equivalence limit of 0.8–1.25 for AUC and $C_{max}$.

The ratios of the mean $C_{max}$ and $AUC_{0-\infty}$ values of deramciclane were 1.24 (90% CI 1.12–1.38) and 1.31 (90% CI 1.21–1.41) in fed versus fasted subjects, which overlapped but exceeded the equivalence limit. In contrast to the parent compound, the 90% CI of the mean ratios for $AUC_{0-\infty}$ and $C_{max}$ of *N*-desmethylderamciclane were within the predefined range.

The 24 and 31% increase in $C_{max}$ and $AUC_{0-\infty}$ of deramciclane, respectively, under fed condition is modest and probably has no clinical significance since it is relatively small compared to the inter-individual variability of these parameters.
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*Keywords:* Deramciclane; Food interaction; Pharmacokinetics; Acid labile; Clinical study

## 1. Introduction

Deramciclane fumarate (EGIS-3886) ((1R, 2S, 4R)-(−)-*N,N*-dimethyl-2-{(1,7,7-trimethyl-2-phenylbicyclo-[2,2,1]-hept-2-yl)oxy}-ethamine-2-(E)-butendioate (1:1); Fig. 1) is a novel anxiolytic compound synthesised by EGIS Pharmaceuticals Ltd (Budapest, Hungary). Compared to benzodiazepines and buspirone, deramciclane differs in its mode of action. In vitro receptor binding studies have shown potent and relatively specific affinity of the drug to $5HT_{2A}$ and $5HT_{2C}$ receptors [1–3]. In addition, the brain $5HT_{2A}$ receptor occupancy of deramciclane has been confirmed in healthy volunteers in a positron emission tomography study [4]. In several animal models, the administration of deramciclane has produced anxiolytic activity without sedative or muscle relaxant effects at therapeutic doses [2,5]. Furthermore, the pharmacokinetic properties of deramciclane have been intensively studied in different animal species with substantial inter-species variation being observed in the pharmacokinetics of the compound [6–10]. Clinical phase I studies have provided evidence regarding safety and tolerability of deramciclane, after single doses up to 150 mg [11] and multiple doses up to 60 mg b.i.d. [12].

In vitro studies have demonstrated the acid-labile nature of deramciclane. Practically no degradation occurred at pH ≥ 3; the compound proved to be quite stable at pH 2.1; however, the degradation rate constant increased approximately 10-fold as the medium pH was reduced from 2.1 to 1.2

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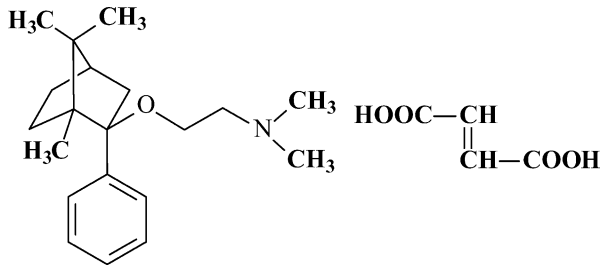


Fig. 1. Chemical structure of deramciclane fumarate.

[13]. In a comparative human pharmacokinetic study, the bioavailability of deramciclane was significantly higher from an enteric-coated tablet as compared to conventional tablets [13]. Yet, the clinical significance of this difference is considered negligible. In contrast, enteric-coated and conventional formulations proved to be bioequivalent in dogs, which could be due to the different anatomy and physiology of the gastro-intestinal tracts of the two species [13].

When performing pharmacokinetic studies of a new pharmaceutical compound, the possibility of drug–food interaction is usually addressed. It is not unusual for meals to interact with drug product and, consequently, modify its pharmacokinetic properties [14]. Moreover, food has been reported to decrease the bioavailability of acid-labile compounds such as penicillin and erythromycin [15,16]. Taking into consideration the acid-labile nature of deramciclane, a food-effect bioavailability study was designed and performed. The aim of this work was to investigate the possibility of high fat containing breakfast effect on the pharmacokinetic parameters of deramciclane conventional tablets.

## 2. Materials and methods

### 2.1. Study design

The study was performed in a randomised, two-way crossover, single-dose design with two-week wash-out period between the drug administrations. The study protocol was approved by the Hungarian National Institute for Pharmacy and the Local Ethical Committee of Haynal Imre University of Health Sciences. The study was conducted in accordance with the Declaration of Helsinki (South Africa Amendment 1996) and each volunteer provided informed consent before entering the study.

Eighteen healthy Caucasian non-smoking male volunteers, ranging from 18 to 40 years of age, and body mass index within 19–26 kg/m$^2$ were enrolled in the study. Health was evaluated by medical history, physical examination, ECG and clinical laboratory tests including HIV, hepatitis B and C tests and urine drug screen within two weeks prior to inclusion to the study. The volunteers were not allowed to use any medication within two weeks and alcohol within 48 h preceding the treatment as well as during the entire study. Ingestion of beverages containing xanthine and chocolate was prohibited 48 h preceding and following drug administration. The volunteers had to avoid excessive physical exercises all over the study.

Eligible subjects were admitted to the study site on the day before dose administration on each of the two treatment periods. From 10 p.m. the volunteers were not allowed to take any food and drink except water. The subjects received single 30 mg dose of deramciclane with 200 ml of water 10 min after the completion of a high-fat breakfast (test treatment) and under fasting condition (reference treatment) according to balanced Latin square design.

The standardised high-fat breakfast consisted of two eggs and one slice of bacon (50 g), served with two slices of white bread (100 g) and with 250 ml of milk (of 3.3% fat content) contained 41.85 g of fat, 38 g of protein, and 65.6 g of carbohydrates with caloric value of 3307 kJ = 787 kcal, which was based on the recommendation of FDA [17] but adapted to the Hungarian nutritional habits. The breakfast had to be consumed in less than 20 min.

All subjects received a standardised lunch and supper 4 and 10 h after dosing, respectively.

Safety assessments were performed pre-dose and up to 96 h post dose. A post study evaluation was performed after the second treatment period.

### 2.2. Sample collection and analysis

Blood samples of 7.5 ml each was collected by venous puncture into S-Monovettes® Syringe, Sarstedt (Nümbrecht, Germany) containing EDTA as an anticoagulant at the following time points: before and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72 and 96 h after the administration of the drug.

Concentration of deramciclane and *N*-desmethylderamciclane in plasma were determined by a validated HPLC–MS/MS method with quantification limit (LOQ) of 0.07 ng/ml for both deramciclane and *N*-desmethylderamciclane [18]. The method involved liquid/liquid extraction. Bioanalytical work was conducted at the Pharmacokinetic Laboratory of the Institute of General and Analytical Chemistry, Budapest University of Technology and Economics, Hungary.

### 2.3. Pharmacokinetic analysis

The pharmacokinetic parameters were determined from the plasma concentration–time data using model independent methods using Kinetika™ Ver. 2.01 validated pharmacokinetic software package (InnaPhase, Champs sur Marne, France). The maximum plasma concentration ($C_{max}$) and the time to reach the maximum plasma concentration ($t_{max}$) were determined from the observed values. The area under the plasma concentration–time curve from time 0 to the last measurable time point ($AUC_{0-t}$) was calculated

by the trapezoidal rule. The area under the plasma concentration–time curve from time 0 extrapolated to infinity was calculated according to the Eq. (1), where $C_t$ and $\beta$ represent the observed plasma concentration at the last measurable sampling time and the elimination rate constant, respectively. The elimination rate constant was determined as the negative of the slope at the log-linear terminal part of the plasma concentration–time curve using linear regression.

$$AUC_{0-\infty} = AUC_{0-t} + C_t/\beta \quad (1)$$

The mean residence time (MRT) was calculated using Eq. (2), where AUMC is the area under the first moment curve.

$$MRT = AUMC/AUC_{0-\infty} \quad (2)$$

### 2.4. Statistical analysis

Following log transformation, $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$ were compared by using four-way analysis of variance for treatment, period, subject (sequence) and sequence.

Log transformed parameters of deramciclane and *N*-desmethylderamciclane administered to the subjects in fed condition (test treatment) were compared to those in the fasted condition (reference treatment) using the Schuirmann test. The geometric least square mean of the fed/fasted ratio and the 90% confidence interval (90% CI) around the ratio were calculated.

Food effect on the bioavailability was indicated if the 90% CI for the ratio of geometric means of fed and fasted treatments was not contained in the equivalence limit of 0.8–1.25 for AUC and $C_{max}$.

The $t_{max}$ values were analysed by non-parametric ranking Wilcoxon's statistical test.

## 3. Results

A total of 19 subjects were enrolled to the study. One subject withdrew from the study just before the drug administration in the first treatment period because of a viral infection. The demographic data of the volunteers which completed the study are shown in Table 1.

The compound was very well tolerated under both fed and fasting states. No subject had any clinically important alteration in vital signs, ECG and clinical chemistry parameters.

Mean plasma concentration–time curve for deramciclane and *N*-desmethylderamciclane are shown in Figs. 2 and 3, respectively. Table 2 summarises the pharmacokinetic parameters of deramciclane and *N*-desmethylderamciclane under fed and fasted conditions. In accordance with the previous human studies, the pharmacokinetic parameters of the compound have substantial inter-individual variability, which can be observed both in fed and in fasted state.

Table 1
Demographic data of the healthy volunteers participated in the study

| Subject no. | Age (year) | Height (cm) | Weight (kg) | BMI (kg/m$^2$) |
|---|---|---|---|---|
| 01 | 25 | 182 | 75.0 | 22.6 |
| 02 | 26 | 170 | 67.0 | 23.2 |
| 03 | 22 | 174 | 64.0 | 21.1 |
| 04 | 19 | 185 | 78.0 | 22.8 |
| 05 | 23 | 186 | 80.0 | 23.1 |
| 06 | 23 | 177 | 78.5 | 25.1 |
| 07 | 20 | 180 | 83.0 | 25.6 |
| 08 | 19 | 192 | 86.0 | 23.3 |
| 09 | 20 | 178 | 67.0 | 21.2 |
| 10 | 21 | 188 | 82.0 | 23.2 |
| 11 | 22 | 174 | 70.0 | 23.1 |
| 12 | 22 | 193 | 75.0 | 20.1 |
| 13 | 24 | 172 | 68.0 | 23.0 |
| 14 | 23 | 176 | 72.0 | 23.2 |
| 15 | 24 | 183 | 65.0 | 19.4 |
| 16 | 32 | 176 | 73.5 | 23.7 |
| 17 | 22 | 176 | 71.0 | 22.9 |
| 18 | 19 | 177 | 69.0 | 22.0 |
| Mean ± SD | 22.6 ± 3.1 | 179.9 ± 6.5 | 73.56 ± 6.36 | 22.70 ± 1.49 |

BMI, body mass index.

The 90% CI around the geometric mean ratio for $AUC_{0-\infty}$ and $C_{max}$ of deramciclane overlapped but ranged outside the predefined 0.8–1.25 region. Similar results were found using the Schuirmann's test. At the same time $t_{max}$ did not change significantly using Wilcoxon's test (Table 3).

Contrary to the parent compound, the ratio for the geometric mean for $AUC_{0-\infty}$ and $C_{max}$ of *N*-desmethyderamciclane fell within the 0.8–1.25 region and no statistically significant difference between the two administration was found in the Schuirmann's test. The $t_{max}$ values increased significantly in fed condition according to the Wilcoxon's test (Table 4).

Elimination half-life and MRT did not change upon food ingestion either for deramciclane or for its *N*-desmethyl metabolite.

## 4. Discussion

Food can influence the absorption, metabolism and elimination of drugs by complex mechanisms [19,20]. Food may decrease the bioavailability of certain drugs by forming a mechanical barrier on the gut wall [21] or by physical binding between drug molecules and food constituents [22,23]. Dietary components, especially fat increase the secretion of bile which enhances the absorption of lipid soluble compounds [24]. Food ingestion increases splanchnic blood flow, and therefore the first-pass hepatic clearance of the drugs with high hepatic extraction ratio may decrease [25]. Food is able

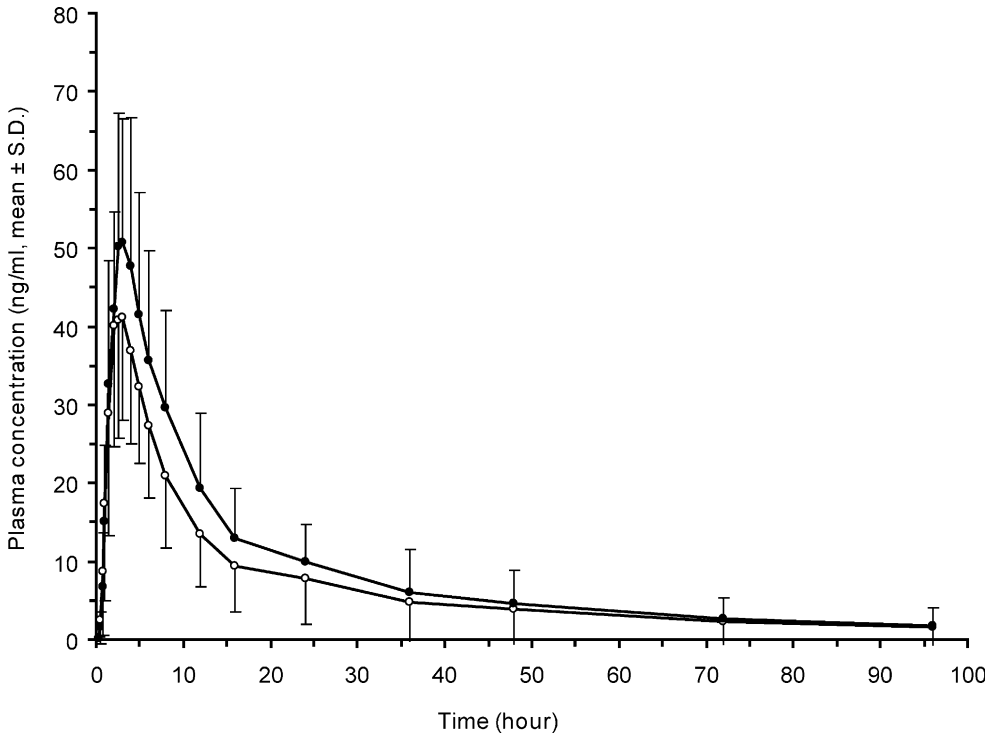


Fig. 2. Pharmacokinetic profile of deramciclane under fasted and fed condition after oral administration of 30 mg deramciclane ($n = 18$, mean ± SD). ●– ●, fed; ○–○, fasted.

to modify the pH of urine and alter the elimination of certain drugs. As a result of increasing gastric transit time and gastric acid exposure in the stomach, food can reduce the bioavailability of some acid-labile compounds.

The instability of deramciclane at low gastric pH and the different bioavailability of the compound after administration of enteric-coated and conventional tablets indicated that food might modify the bioavailabilty of the compound

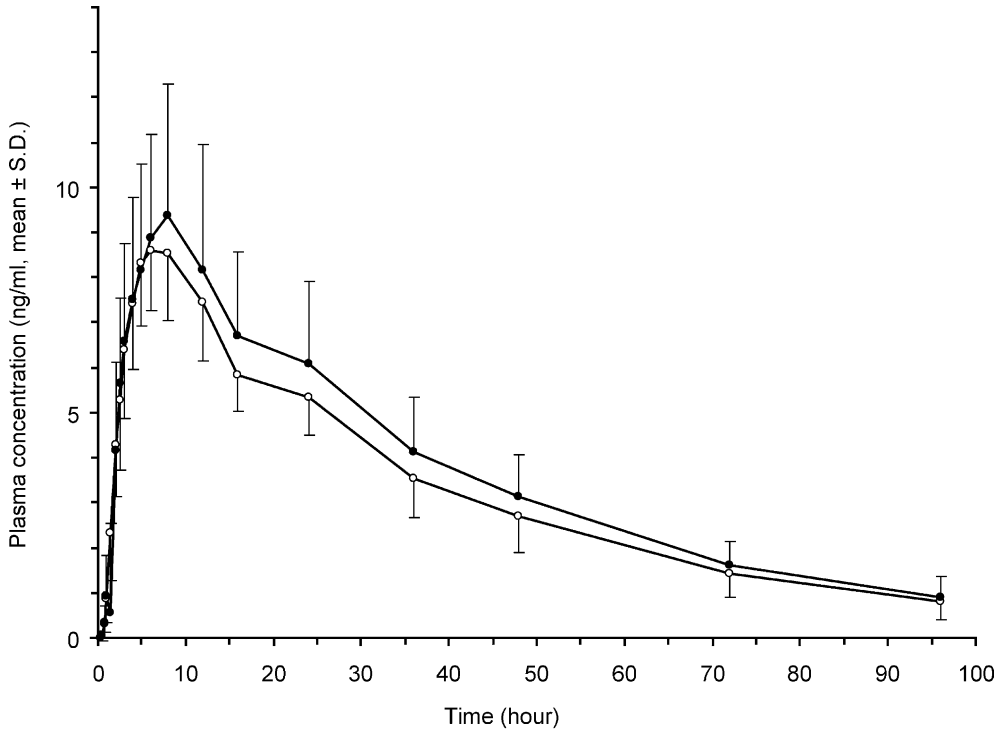


Fig. 3. Pharmacokinetic profile of *N*-desmethylderamciclane under fasted and fed condition after oral administration of 30 mg deramciclane ($n = 18$, mean ± SD). ●–●, fed; ○–○, fasted.

Table 2
Pharmacokinetic parameters for deramciclane and *N*-desmethylderamciclane under fed and fasted conditions ($n = 18$; mean ± SD)

| Pharmacokinetic parameters | Deramciclane | | *N*-desmethylderamciclane | |
|---|---|---|---|---|
| | Fed | Fasted | Fed | Fasted |
| $C_{max}$ (ng/ml) | 54.2 ± 17.9 | 43.7 ± 15.1 | 9.4 ± 2.9 | 8.9 ± 1.28 |
| $t_{max}$ (h) | 3.17 ± 0.89 | 2.69 ± 0.52 | 7.89 ± 1.84 | 6.11 ± 1.28 |
| $AUC_{0-t}$ (ng h/ml) | 837.2 ± 452.3 | 658.0 ± 454.6 | 352.6 ± 93.0 | 314.4 ± 57.3 |
| $AUC_{0-\infty}$ (ng h/ml) | 945.7 ± 629.2 | 745.7 ± 629.2 | 394.6 ± 109.6 | 348.6 ± 78.9 |
| $t^{\beta}_{1/2}$ (h) | 30.13 ± 8.16 | 30.82 ± 7.91 | 28.23 ± 9.02 | 27.32 ± 5.75 |
| MRT (h) | 31.41 ± 12.33 | 31.77 ± 10.87 | 42.5 ± 12.4 | 40.50 ± 8.13 |

[13]. In the present study food effect on bioavailability of deramciclane was indicated, since the 90% CI of the mean ratio for $C_{max}$ and $AUC_{0-\infty}$ of deramciclane in fed versus fasted subjects was overlapped but ranged to the outside of the predefined 0.8–1.25 region. The time to the maximum plasma concentration ($t_{max}$) values for deramciclane remained unchanged. In case of *N*-desmethyl metabolite, food did not significantly influence any pharmacokinetic parameters, except for the $t_{max}$ value.

The observed increase in the bioavailablity of deramciclane has probably no clinically significant consequence. In former human study $AUC_{0-\infty}$ and $C_{max}$ parameters showed high intersubject variability [11], and in the present study the range of $AUC_{0-\infty}$ and $C_{max}$ values in the fasted state was 8.2-fold (387–3163 h ng/ml) and 3.4-fold (24.8–84.8 ng/ml), respectively. The 31% increase in $AUC_{0-\infty}$ and 24% increase in $C_{max}$, observed after the food consumption seem to be small comparing to such variabilities. In addition, deramciclane proved to be very safe in human phase I studies in dose clearly higher than the expected therapeutic dose. Therefore, increase in the bioavailabity of the compound might not have safety consequences either.

Our results differ from those already collected regarding other acidic labile compounds (e.g. erythromycin) which showed decreasing bioavailability when administered with food. One possible explanation of this discrepancy could be, that in case of erythromycin the instability is observed under pH 5 [26]. In fasting state the mean gastric pH is between 1.1 and 1.5 [27]. Briefly after consumption of food the gastric pH is elevated up to 6.7, then decline back to the value of the fasting condition over a period less than 2 h [28]. As food increase the gastric transit time [29], erythromycin molecules remain for more prolonged time in a $pH < 5$ which might cause increased degradation.

Table 3
Statistical comparison of pharmacokinetic parameters for deramciclane under fed and fasted conditions

| Statistical tests | Reference range | Pharmacokinetic parameters | | | |
|---|---|---|---|---|---|
| | | $C_{max}$ | $AUC_{0-t}$ | $AUC_{0-\infty}$ | $t_{max}$ |
| Point estimate of ratio | 0.8–1.25 | 1.24 | 1.31 | 1.30 | – |
| 90% Confidence interval | 0.8–1.25 | 1.12–1.38 | 1.21–1.41 | 1.21–1.41 | – |
| Schuirmann test | $t_1; t_2 > 1.75$ | −1.07 (S); 11.44 (NS) | −0.95 (S); 10.9 (NS) | 0.13 (S); 7.43 (NS) | – |
| Wilcoxon test | $M > 35$ | – | – | – | 41 (NS) |

S, significant difference; NS, non-significant difference; $t_1$, $t_2$, values of the Student *t*-test; *M*, value of the Wilcoxon test.

Table 4
Statistical comparison of pharmacokinetic parameters for *N*-desmethylderamciclane under fed and fasted conditions

| Statistical tests | Reference range | Pharmacokinetic parameters | | | |
|---|---|---|---|---|---|
| | | $C_{max}$ | $AUC_{0-t}$ | $AUC_{0-\infty}$ | $t_{max}$ |
| Point estimate of ratio | 0.8–1.25 | 1.01 | 1.11 | 1.12 | – |
| 90% Confidence interval | 0.8–1.25 | 0.93–1.11 | 1.03–1.19 | 1.04–1.20 | – |
| Schuirmann test | $t_1; t_2 > 1.75$ | 2.89 (NS); 7.69 (NS) | 2.84 (NS); 8.65 (NS) | 4.22 (NS); 4.80 (NS) | – |
| Wilcoxon test | $M > 21$ | – | | – | 4 (S) |

S, significant difference; NS, non-significant difference; $t_1$, $t_2$, values of the Student *t*-test; *M*, values of the Wilcoxon test.

Contrary to erythromycin, the critical pH for the instability of deramciclane is about 2, therefore the postprandial elevation of the gastric pH prevents the degradation of deramciclane for longer time period.

This theory is supported by the fact that in previous study, where deramciclane bioavailability of enteric-coated and conventional tablet was compared, the 90% CI for the geometric mean ratio of $AUC_{0-\infty}$ and $C_{max}$ (1.24–1.39 and 1.13–1.27, respectively) [13] closely resembled the values measured in this study. This indicates that the underlining mechanism in the increase of the bioavailability after food consumption could be decreased degradation of deramciclane in the higher pH of gastric juice. In addition the absorption of deramciclane from the gastro-intestinal tract is almost complete [8], and the anticipated difference in oral bioavailability of the drug would be reasonably attributed to food effect on gastric conditions rather than on drug absorption itself.

In conclusion food has only slight effect on the bioavailability of deramciclane, which probably has no clinical significance, therefore it is reasonable to assume that the drug can be given with food without any restrictions. In addition, our results indicate that not all acid-labile compounds behave similarly when they are given with food. The effect of meal on the pharmacokinetics of such compounds depend on the value of the critical pH where the acid instability occurs.

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