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Important Update:

In order to remain compliant with the most current regulatory guidelines, we have updated the labeling on our SR formulations from Buprenorphine and Meloxicam SR to Buprenorphine and Meloxicam in Polymer. **As of April 1, 2024, SR preparations mentioned in the attached study are now labeled as in Polymer**, with no changes to the formulation of the medication(s).

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Pharmacokinetics of Sustained-release, Oral, and Subcutaneous Meloxicam over 72 Hours in Male Beagle Dogs

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In cynomolgus macaques, plasma levels of sustained-release formulations of meloxicam meet or exceed efficacious concentrations for 48 to 72 h, thereby allowing less animal handling and providing more consistent efficacy than standard formulations of meloxicam. The goal of this study was to compare the pharmacokinetics of a single subcutaneous dose of a sustained-release formulation of meloxicam (Melox-SR) with those of oral (Melox-PO) and standard subcutaneous (Melox-SC) formulations dosed every 24 h for 3 consecutive days. Dogs (5 or 6 adult male Beagles) each received the following 3 treatments: first, Melox-SR (10 mg/mL, 0.6 mg/kg SC once), next Melox-SC (0.2 mg/kg SC once, followed by 0.1 mg/kg SC every 24 h), and finally Melox-PO (same dosage as Melox-SC), with a washout period of at least 2 wk between formulations. Blood was collected at 0 (baseline), 1, 4, 8, 12, 24, 48, and 72 h after the initial administration of each formulation for comparison of meloxicam plasma concentrations. Blood was also collected before administration and at 48 h after Melox-SR injection for CBC and chemistry analysis. Plasma concentrations (mean ± 1 SD) of Melox-SR peaked at the 1-h time point (2180 ± 359 ng/mL), whereas those of Melox-PO (295 ± 55 ng/mL) and Melox-SC (551 ± 112 ng/mL) peaked at the 4-h time point. Melox-SR yielded significantly higher plasma concentrations than Melox-PO and Melox-SC until the 48 and 72-h time points, respectively. Melox-SC plasma concentrations were significantly higher than those of Melox-PO at 4, 8, 12, 24, 48 and 72 h. No lesions were noted at the Melox-SR injection sites, and Melox-SR administration was not associated with changes in the CBC and serum chemistry panels. A single 0.6-mg/kg dose of Melox-SR can yield plasma concentrations that exceed 350 ng/mL for at least 72 h in adult male dogs.

Abbreviations: Melox-PO, oral meloxicam; Melox-SC, subcutaneous meloxicam; Melox-SR, sustained-release formulation of meloxicam

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Meloxicam, a preferential inhibitor of cyclooxygenase 2 (COX2) in the oxicam family,[1,5] is one of the most commonly used NSAID in dogs due to its relatively long half-life and limited gastrointestinal adverse effects.[5] Inhibition of COX2 decreases prostaglandin synthesis and blocks the arachidonic acid cascade centrally and peripherally, thereby providing analgesic, antiinflammatory, and antipyretic effects.[6]

Meloxicam is commonly given every 12 to 24 h, reaching steady-state concentrations in 3 to 4 d, with a half-life of 17 to 24 h in dogs.[3-5] Prior to achieving steady state, meloxicam's plasma concentrations normally increase after administration of a daily dose and then decrease over time until the next dose is given, thus providing a more cyclically variable plasma concentrations of drug and possibly resulting in inconsistent efficacy.[2] In cynomolgus macaques, a new sustained-release formulation of meloxicam (Melox-SR) has been shown to achieve plasma concentrations that exceed purported therapeutic levels for 48 to 72 h.[2] To date, no published pharmacokinetic data regarding Melox-SR in dogs have been published. Melox-SR is composed of a liquid biodegradable polymer with biocompatible organic solvents in combination with the FDA-approved pharmaceutical-grade meloxicam. Once administered, the polymer in the solution precipitates or coagulates upon contact with aqueous body fluid to form a sustained release delivery matrix. The sustained release of meloxicam from an injection of Melox-SR may provide prolonged effective plasma concentrations, thus potentially minimizing handling during immediate postoperative period.[7] Therefore, Melox-SR can be advantageous over regular formulations of meloxicam by lowering the necessary frequency of administration and providing more consistent efficacy.

This study evaluated 3 formulations of meloxicam—oral meloxicam (Melox-PO), standard subcutaneous meloxicam (Melox-SC), and Melox-SR—in adult male dogs to compare the plasma concentrations of each formulation over 72 h. The goal was to determine whether Melox-SR provided longer duration of efficacious plasma concentrations than the other 2 formulations.

Materials and Methods

Animals. Intact, purpose-bred, male beagle dogs ($n = 7$; age, 5 to 6 y; weight, 10 to 15 kg; Ridglan Farms, Mt Horeb, WI) were used in this study. An acclimation period of 5 d was provided to all dogs, and dogs were healthy on physical examination prior to initiation of the study. Unless separation was required for veterinary purposes, all dogs were pair-housed in kennels under a 12:12-h light cycle. Dogs were fed standard commercial

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food (Adult Dog Exclusive Chicken and Rice, PMI Nutrition, Denver, CO) once daily and provided with ad libitum access to water. Dogs were cared for in an AAALAC-accredited facility, and the study was approved by the IACUC of Colorado State University.

Study design. Melox-PO (Metacam 1.5 mg/mL, Boehringer Ingelheim, St Joseph, MO) and Melox-SC (Metacam 5 mg/mL, Boehringer Ingelheim) formulations were administered according to the manufacturer's recommendations of 0.2 mg/kg for the initial dose followed by 0.1 mg/kg once daily for 2 more days. Melox-SR (Meloxicam SR 10 mg/mL, ZooPharm, Windsor, CO) was administered subcutaneously as a single 0.6-mg/kg dose. All subcutaneous injections were administered between the scapulae. Dogs first received Melox-SR followed by a 2-wk washout period, then Melox-SC followed by a 3-wk washout period, and finally Melox-PO. The prolonged washout period was due to a delay in the study between the Melox-SC and Melox-PO groups. We chose not to randomize the study to reduce the number of animals used. One dog developed melena, diarrhea, lethargy, and inappetence after receiving Melox-SR and was removed from the study without receiving Melox-SC or Melox-PO. A replacement dog was added to the Melox-PO group, such that the Melox-SR and Melox-PO groups each had 6 dogs per group, but because the replacement dog was not available in time, the Melox-SC group had only 5 dogs. All dogs were weighed prior to each round of dosing, and drug volumes were adjusted.

Dogs were manually restrained for cephalic venipuncture of alternating legs. A 2-mL blood sample was collected into an EDTA tube at 0 (baseline [predose]), 1, 4, 8, 12, 24, 48, and 72 h after initial drug administration. The 24-, 48-, and 72-h blood samples were collected before administration of the next dose and represent the nadir. Blood for CBC and chemistry analysis was collected before and at 48 h after the initial Melox-SR injection. Dogs were assessed for injection site reactions at each blood collection time point, and physical examinations were completed at the 72-h time point.

Analysis of meloxicam plasma concentration. Blood for analysis of plasma meloxicam concentration was immediately placed into an EDTA collection tube and refrigerated until centrifugation. The blood was centrifuged at 10,000 × g for 10 min. The plasma was immediately removed and then stored at -80 °C until analysis.

Plasma concentrations of meloxicam were measured by using liquid chromatography and tandem mass spectrometry. Briefly, 50 µL of each plasma sample was mixed with 50 µL of the internal standard (250 ng/mL meloxicam-d_3 in 50:50 water:methanol) followed by 150 µL acetonitrile to precipitate the protein. Samples were vortexed for 3 min and centrifuged for 10 min at 20,000 × *g*; 20 µL of supernatant was removed from each well, added to 120 µL of water in the well of a new 96-well plate, vortexed for 1 min, and centrifuged at 20,000 × *g* for 2 min at room temperature. Samples were separated on LC-20A HLPC (Shimadzu, Kyoto, Japan) and Triple-Quad 4000 devices (ABSciex, Toronto, Canada) using Poroshell 120 EC-C18 analytical columns (Agilent, Santa Clara, CA) at a temperature of 40 °C. Calibration and quality controls were conducted, and a standard curve with the quantitation range of 5 to 6250 ng/mL was made. The LC–MS method for meloxicam yielded a calibration standard curve of $1 / x^2$ with an R^2 value of 0.9987. Calibration curve points (11 of 12, 92%) and quality controls (12 of 12, 100%) were within the specified 15% error for both precision and accuracy.

Pharmacokinetic analysis. Noncompartmental analyses were used to calculate the pharmacokinetic parameters. The peak concentration (C_{max}) and time at peak concentration (t_{max}) values were obtained from the data. The elimination rate (K_{el}) was calculated by using logarithmic–linear regression of the plasma concentration–time curve. The half-life ($t_{1/2}$) of Melox-SR was calculated between the 4- and 24-h time points. AUC was calculated by using the trapezoidal rule and extrapolated to infinity by using the rate constant of the terminal elimination phase.

Statistics. By using statistical analysis software (Prism 8.00 for Windows, GraphPad Software, La Jolla, CA), repeated-measures 2-way ANOVA with Tukey multiple-comparisons testing was completed for pharmacokinetic analysis. Repeated-measures 2-way ANOVA with Sidak multiple-comparison testing was completed to compare hematologic parameters collected before and after the administration of Melox-SR. Values that were below the limit of detection of the pharmacokinetic assay were replaced with 0 ng/mL, which occurred only at baseline. The fixed effects included time (0, 1, 4, 8, 12, 24, 48, and 72 h) and treatment (Melox-SR, Melox-SC, Melox-PO). A *P* value less than 0.05 was considered statistically significant.

Results

Pharmacokinetics. The plasma concentrations of 3 meloxicam formulations were determined in male dogs over a 72-h period (Figure 1). Baseline blood samples (0 h) demonstrated no detectable meloxicam in the plasma after the washout period. Melox-SR was given once subcutaneously, and Melox-PO and Melox-SC formulations were dosed every 24 h. The plasma concentration curve for Melox-SR peaked at 1 h after administration (2180 ± 359 ng/mL) and steadily decreased to 427 ± 64 ng/mL by the 72-h time point. Melox-PO peaked at 4 h after administration (295 ± 55 ng/mL) and steadily decreased to 181 ± 27 ng/mL at 24 h. Samples for the 48- and 72-h time points were collected immediately before administration of the next dose, and represent the nadirs (199 ± 35 and 225 ± 62 ng/mL, respectively). Melox-SC also peaked at 4 h after administration (551 ± 112 ng/mL), steadily declined to 431 ± 66 ng/mL at the 24-h time point, and remained near that concentration for the 48- and 72-h time points (469 ± 80 and 433 ±43 ng/mL, respectively).

Melox-SR yielded a significantly higher plasma concentration than Melox-SC at the 1-, 4-, 8-, 12-, 24- ($P < 0.0001$), and 48-h ($P = 0.0325$) time points. In addition, Melox-SR plasma concentrations were higher than those of Melox-PO at 1, 4, 8, 12, 24, 48, ($P < 0.0001$), and 72 h ($P = 0.02$). Melox-SC had a significantly higher plasma concentration than Melox-PO at 4 ($P = 0.003$), 8 ($P = 0.007$), 12 ($P = 0.003$), 24 ($P = 0.004$), 48 ($P = 0.002$), and 72 h ($P = 0.02$).

The noncompartmental analysis for the 3 formulations are summarized in Table 1. The $AUC_{0–72}$ for Melox-SR was calculated (82,198 µg × h/mL) and extrapolated to infinity (99,990 µg × h/mL) with 18% extrapolation. The $AUC_{0–24}$ for Melox-SR, Melox-SC, and Melox-PO were 41,938, 10,620, and 5095 µg × h/mL, respectively. The $t_{1/2}$ for Melox-SR was 54.8 h.

Animal wellbeing. No lesions were noted at injection sites after administration of Melox-SR or Melox-SC. Injection sites were monitored throughout the study, at all collection time points. Because Melox-PO was administered last, all injection sites were monitored for at least 3 wk after the last Melox-SC injection and for 6 wk after Melox-SR injection. Baseline serum chemistry and CBC values were within normal limits for all animals prior to Melox-SR administration. At 48 h after the administration of Melox-SR, one dog developed clinical signs of melena, diarrhea, lethargy, and inappetence. Serum chemistry

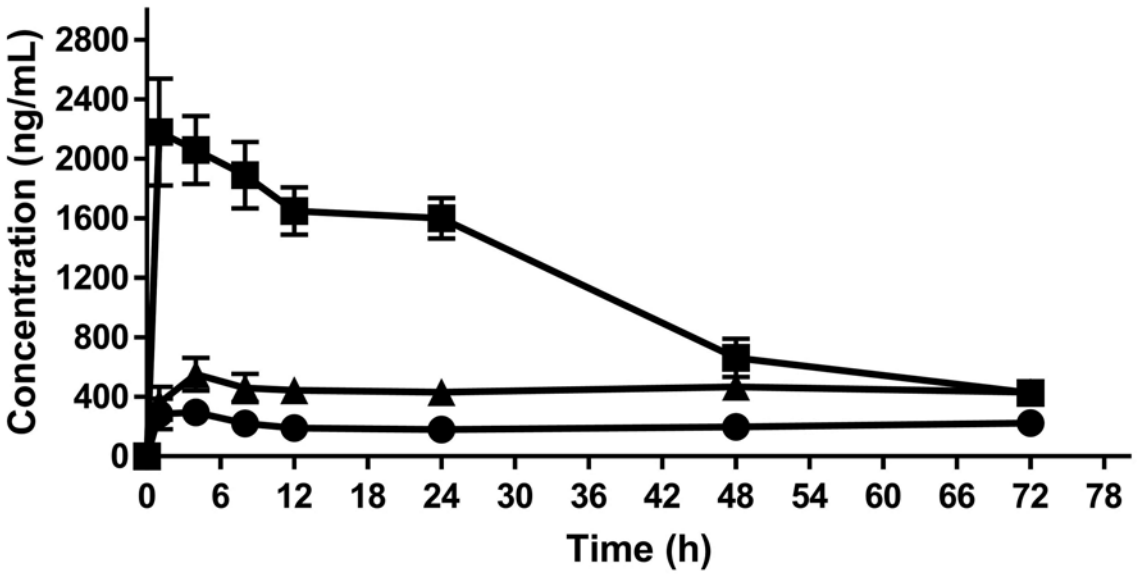

Figure 1. Plasma concentration (mean ± 1 SD [error bars]) of meloxicam after dosing with Melox-SR (n = 6, squares), Melox-SC (n = 5, triangles), and Melox-PO (n = 6, circles) in adult male beagles. Melox-PO and Melox-SC samples were collected prior to subsequent drug administrations at the 24- and 48-h time points. Plasma concentrations at these time points represent the nadirs.

(Table 2) and CBC (Table 3) measurements were repeated for all dogs at the 48 h time point and showed that, except for the dog with clinical signs, all hematologic parameters remained within normal ranges. The dog with clinical signs had hypoglycemia (34 mg/dL), low BUN (4 mg/dL), low creatinine (0.3 mg/dL), hypocholesterolemia (122 mg/dL), and slightly elevated creatine kinase (364 IU/L) and AST (55 IU/L), consistent with small intestinal-hemorrhage and inappetence. This dog was removed from the study and was diagnosed at necropsy with small intestinal leiomyosarcoma. Average values for CBC and clinical chemistry parameters before and after Melox-SR administration did not differ except for glucose (P = 0.005), due to the dog with leiomyosarcoma.

Discussion

This study compared the pharmacokinetics of Melox-SR with those of Melox-SC and Melox-PO formulations over 72 h in 7 male beagle dogs. Results showed that the plasma concentration of Melox-SR peaked at 1 h after administration and stayed above those of Melox-SC and Melox-PO, with dogs dosed according to the manufacturer's drug label for the entire 72 h.[3] A single dose of Melox-SR provides a prolonged period of elevated plasma drug concentrations, compared with Melox-SC and Melox-PO.

Pharmacokinetic findings for Melox-SC and Melox-PO in the present study are similar to previous studies assessing the pharmacokinetics of meloxicam in dogs.[2-4,9,14] Melox-SC and Melox-PO plasma concentrations peaked at 4 h after injection, similar to previous reports.[4,14] C_{max} was higher for Melox-SC (551 ng/mL) than Melox-PO (295 ng/mL), consistent with previous literature and most likely due to differences in absorption.[4] The C_{max} and T_{max} values for Melox-SC and Melox-PO that were determined in this study may be inaccurate due to the few blood collection time points. Furthermore, we did not note fluctuation of the Melox-SC and Melox-PO plasma concentrations because blood samples were collected only immediately before repeated administration of the drugs. Consequently, the pharmacokinetic curves demonstrate the nadir plasma concentrations, which information may be particularly important when assessing analgesia between doses. In this study, we calculated the AUC_{0-72} for Melox-SR only, because corresponding data for Melox-SC and Melox-PO would be falsely low because their plasma concentration curves did not include time points between the 24-, 48-, and 72-h collections.

Table 1. Noncompartmental pharmacokinetic analysis in dogs treated with Melox-SR (n = 6), Melox-SC (n = 5), and Melox-PO (n = 6)

	Melox-SR	Melox-SC	Melox-PO
C_{max} (ng/mL)	2180	551	295
t_{max} (h)	1	4	4
$t_{1/2}$ (h)	54.8	NA	NA
AUC_{0-72} (μg × h/mL)	82198	NA	NA
$AUC_{0-\infty}$ (μg × h/mL)	99990	NA	NA

NA, not applicable

Previous studies showed that Melox-SC and Melox-PO have the same $t_{1/2}$, i.e., 17 to 24 h.[2-4] These previous studies calculated $t_{1/2}$ by using a single dose, thus allowing for accurate terminal half-life collection. Ideally, $t_{1/2}$ would be calculated from the 'terminal half-life' or after pseudo-equilibrium of distribution has been reached.[11] Because Melox-SC was readministered at 24 h in this study and blood was collected at only a few time points between injections, Melox-SC and Melox-PO $t_{1/2}$ were not calculated.

Meloxicam is a selective COX2 inhibitor, meaning that it preferentially inhibits COX2 but can inhibit COX1 at higher doses.[8,10,13] The minimum effective concentrations of meloxicam for COX1 and COX2 enzymes in humans are estimated to be 2000 ng/mL (5.7 μM) and 80 ng/mL (0.23 μM), respectively.[13] If the minimum effective concentration of meloxicam for COX1 is similar between dogs and humans, Melox-SR administration to dogs might inhibit COX1, leading to decreased gastrointestinal protection and increased risk of mucosal ulceration.

One dog had clinical signs of melena, diarrhea, and lethargy after Melox-SR administration and was later diagnosed with a small intestinal leiomyosarcoma. Bloodwork and physical exam findings were unremarkable before administration of Melox-SR. The high concentration of meloxicam (2180 ng/mL) associated with Melox-SR administration might have exacerbated the clinical

Table 2. Serum chemistry parameters (mean ± 1 SD) before and after treatment of male beagle dogs with Melox-SR (0.6 mg/kg SC)

	Baseline	After treatment	Reference range
Sodium (mEq/L)	145.2 ± 1.5	146.2 ± 0.8 (149)	142–152
Potassium (mEq/L)	4.5 ± 0.3	4.6 ± 0.2 (4.28)	3.9–5.4
Chloride (mEq/L)	110.5 ± 1.9	113.0 ± 1.3 (116)	108–118
BUN (mg/dL)	13.3 ± 2.9	15.0 ± 4.2 (4)	7–30
Creatinine (μM)	0.68 ± 0.13	0.64 ± 0.05 (0.3)	0.6–1.6
Glucose (mM)	91.0 ± 6.2	82.0 ± 8.9 (34)	70–115
Total protein (g/dL)	6.2 ± 0.3	6.1 ± 0.2 (5.9)	5.0–7.0
ALP (U/L)	39.7 ± 9.9	38 ± 9.7 (72)	15–140
AST (U/L)	28.7 ± 8.0	38.6 ± 3.8 (55)	15–45
ALT (U/L)	48.5 ± 23.0	54.8 ± 20.3 (40)	10–90

Baseline values are averaged from all 6 dogs, whereas posttreatment parameters (blood collected 48 h after Melox-SR administration) are averaged from the 5 dogs without clinical symptoms. Posttreatment parameters within parentheses are from the dog with clinical signs of melena, inappetence, and lethargy after administration of Melox-SR and diagnosed with leiomyosarcoma.

Table 3. CBC parameters (mean ± 1 SD) before and after treatment of male beagle dogs with Melox-SR (0.6 mg/kg SC)

Parameter	Baseline	After treatment	Reference range
Hgb (g/dL)	16.0 ± 0.7	16.8 ± 0.4 (16.7)	13–20
Hct (%)	45.5 ± 2.6	49.2 ± 1.3 (51)	40–55
RBC (10^6/μL)	6.9 ± 0.3	7.2 ± 0.4 (8.0)	5.5–8.5
MCV (fL)	66.8 ± 2.1	67.8 ± 2.3 (64)	62–74
RDW (%)	13.0 ± 0.4	12.4 ± 1.1 (15)	12–15
MCHC (g/dL)	35.0 ± 0.6	34.2 ± 0.6 (33)	33–36
Platelets ($\times10^3$/μL)	363 ± 85	334 ± 68 (359)	200–500
MPV (fL)	9.2 ± 1.1	10.4 ± 1.5 (14.4)	7.5–14.6
Nucleated cells ($\times10^3$/μL)	8.6 ± 2.3	8.7 ± 2.2 (10.3)	4.5–15
Neutrophils ($\times10^3$/μL)	5.8 ± 1.5	5.12 ± 1.9 (7.2)	2.6–11
Lymphocytes ($\times10^3$/μL)	1.8 ± 0.5	2.6 ± 0.6 (1.9)	1–4.8
Monocytes ($\times10^3$/μL)	0.5 ± 0.2	0.5 ± 0.2 (0.8)	0.2–1.0
Eosinophils ($\times10^3$/μL)	0.5 ± 0.3	0.5 ± 0.3 (0.1)	0.1–1.2
Basophils ($\times10^3$/μL)	0.03 ± 0.07	0.04 ± 0.01 (0)	0–0.1

Baseline values are averaged from all 6 dogs, whereas posttreatment parameters (blood collected 48 h after Melox-SR administration) are averaged from the 5 dogs without clinical symptoms. Posttreatment parameters within parentheses are from the dog with clinical signs of melena, inappetence, and lethargy after administration of Melox-SR and diagnosed with leiomyosarcoma.

signs associated with leiomyosarcoma. Because Melox-SR was the first formulation administered in this study and because the dog was euthanized, we are unable to demonstrate whether this dog would have shown the same clinical signs after Melox-SC and Melox-PO administration.

Previous studies have shown that females metabolize meloxicam differently than males, with females having a longer elimination half-life.[2,4,12] Male beagles were used in the current study to provide the minimum numbers of pharmacokinetic values needed to control for variability among animals. Melox-SC and Melox-PO were administered according to the drug-label instructions (0.2 mg/kg initially, followed by 0.1 mg/kg at 24 and 48 h), and Melox-SR was dosed according to manufacturer recommendations (0.6 mg/kg), similar to a previous study in macaques.[2] Consequently, the Melox-SR total dose was larger than the accumulated doses of Melox-PO and Melox-SC (0.4 mg/kg). Other doses of Melox-SR have not been examined in dogs, and a lower dose may still achieve the minimum therapeutic dose. Although this study was not designed as a safety study, we did not find physical abnormalities in any of the dogs (except the one with the leiomyosarcoma). We did not do a fecal occult blood test, but there were no significant changes in the blood work. However, we cannot rule out the possibility of subclinical effects. Reducing the dose may still provide an adequate plasma concentration of meloxicam and have less potential for subclinical effects.

The same doses of Melox-SC and Melox-PO that we used here were effective in previous studies in dogs.[3] In our current study, Melox-SR reached higher plasma concentrations than did the other formulations at every blood collection time point. Due to repeated dosing of Melox-SC and Melox-PO, the plasma concentrations of these formulations might have surpassed those of Melox-SR between the 24-, 48-, and 72-h time points. Although efficacy was not examined in this study, we expect that Melox-SR would be efficacious for at least 72 h, given that it sustained plasma concentrations above those of Melox-SC and Melox-PO at every time point for the entire 72-h study. Further studies are needed to assess the safety and efficacy of various doses of Melox-SR in a larger population of animals.

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