



Pharmacokinetic Evaluation of Paclitaxel in South Indian Cancer Patients: A Prospective Study

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ABSTRACT

Paclitaxel is a promising drug in the treatment of different solid tumors. It exhibits nonlinear pharmacokinetics, particularly when administered as a constant rate infusion for shorter duration (e.g., 3 h). Because of the nonlinearity, relatively small changes in dose may lead to large changes in peak plasma concentration and total drug exposure. The study was conducted to evaluate the pharmacokinetics of different doses of paclitaxel administered intravenously as an infusion. A prospective study was conducted in 23 cancer patients aged between 28 and 74 years, treated with paclitaxel (130, 200, 230, and 260 mg/m²) over 3 h as constant rate infusion. Plasma samples were collected from all patients at 0, 1, and 3 h and for five patients at 5 and 13 h and paclitaxel concentrations were determined using high-performance liquid chromatography method. The overall mean clearance was found to be 47.5847 ± 142.028 l/h; the mean volume of distribution was 142.028 ± 73.438 l; mean elimination rate constant was 0.336 ± 0.002 /h; mean half-life was 2.086 ± 0.009 h; mean area under the curve (AUC) was 5.5917 ± 2.707 mg/ml*h; and the mean of mean residence time was 2.980 ± 0.0131 h. Paclitaxel showed nonlinear kinetics and the pharmacokinetic parameters calculated were similar to those quoted in the literature. The peak plasma concentration at 130 mg dose level was 2 µ/ml, but an increase in dose was not associated with proportional increase in plasma concentration. No significant difference was found between pharmacokinetic parameters such as clearance, volume of distribution, and AUC at different dose levels.

Key words: Non-linear, pharmacokinetics, plasma concentrations, optimization, taxane

INTRODUCTION

Paclitaxel is a taxane, produced semisynthetically from a precursor found in the leaves of *Taxus baccata*.^[1]

Paclitaxel is a potent anticancer drug.^[2,3] Paclitaxel, with its unique mechanism of action as an inducer of tubulin polymerization, has demonstrated impressive clinical antitumor activity in patients with breast, lung, head, neck, and advanced platinum-refractory ovarian carcinoma. It appears to be one of the most promising agents for the first- or second-line chemotherapy of solid tumors.^[4]

Paclitaxel exhibits nonlinear pharmacokinetics, particularly when the drug is administered over shorter periods of infusion (3 h). Both saturable distribution and elimination

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contribute to the nonlinear disposition of paclitaxel. Because of the nonlinearity of its pharmacokinetics, relatively small changes in dose may lead to large changes in peak plasma concentrations and total drug exposure. Following intravenous administration, paclitaxel is widely distributed into body fluids and tissues. It has a large volume of distribution that appears to be affected by dose and duration of infusion.^[5-9]

Paclitaxel is extensively metabolized in the liver. Metabolism to its major metabolite, 6a-hydroxypaclitaxel, is mediated by cytochrome P-450 isoenzyme CYP2C8, while metabolism to two of its minor metabolites, 3'-p-hydroxypaclitaxel and 6a, 3'-p-dihydroxypaclitaxel, is catalyzed by CYP3A4.35. Paclitaxel and its metabolites are excreted principally in the feces via biliary elimination. Both a reduction in the clearance and an overproportional increase in peak plasma concentration (C_{max}) of paclitaxel are observed with increasing dosages indicative that both drug elimination and distribution were affected.^[10]

Safety and efficacy of paclitaxel have been studied extensively.^[11] However, its complete pharmacokinetic profile in humans has not yet been fully understood. With this in background, pharmacokinetics of paclitaxel has been studied with the objectives of optimizing the dose to achieve desired plateau plasma-drug concentration, to maximize response and reduce toxicity of drug, and to learn what factors affect plasma concentrations in the study population.

MATERIALS AND METHODS

A prospective study was conducted between September 2008 and March 2009, in the medical oncology wards of a 1675-bedded tertiary care teaching hospital in South India, with the approval of the Institutional Ethics Committee (IEC/08/SEP/68/33) and the consent of the study participants. Patients above 18 years of age, with histologically confirmed malignancy and treated with paclitaxel were enrolled in this study.

A detailed data of all the patients were collected which included demographics (age, sex, weight, and height) disease status, smoking habits, alcoholic consumption, family history, co morbidities (Cardiovascular, renal, and hepatic diseases), and medications taken along with paclitaxel.

The patients were administered paclitaxel at the doses of 130, 200, 230, and 260 mg/m² intravenously as constant rate infusion over 3 h. Vials containing 6 mg/ml of

paclitaxel supplied by Feron life sciences (Pacliron), Intas biopharmaceuticals (Cytax), and Macmoham Pharma Ltd. (Amtax) were used for this study. After 3 h of paclitaxel infusion, patients were administered intravenous saline for 3 h. The saline was stopped, and patients were given either one or two of the following drugs cisplatin, carboplatin, and 5-fluorouracil. The patients were also treated with dexamethasone 8 mg intravenous, ranitidine 50 mg intravenous, diphenhydramine 50 mg intramuscular, and palanosetran 0.25 mg in 100 ml of saline over 30 min before starting paclitaxel therapy.

Heparinized blood samples were collected from the patients before starting paclitaxel infusion (0 h) and at the time intervals of 1 and 3 h for all patients; 5 and 13 h for five patients and were stored at -80°C. The extraction of paclitaxel from the biological matrix was carried out by using protein precipitation method.

The plasma concentrations of paclitaxel at various time intervals were determined using high-performance liquid chromatography (HPLC), and pharmacokinetic parameters of paclitaxel at different dose levels were evaluated.

Estimation of plasma concentrations of paclitaxel by HPLC

Paclitaxel estimations by HPLC were conducted at Dr. T M A Pai Bioavailability Center, Manipal College of Pharmaceutical Sciences, Manipal. The estimations were carried out by adapting a validated method stated in "Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies,"^[12] with minor modification as stated in the study done by Alex Sparreboom.^[13]

Materials

1. Paclitaxel: Natco Pharma Ltd. (standard)
2. Celecoxib: Dr. Reddy's Laboratories (Internal standard)
3. Acetonitrile (HPLC grade): E-Merck (India) Limited, Mumbai.
4. Methanol (HPLC grade): E-Merck (India) Limited, Mumbai.
5. Glacial acetic acid (GR grade): E-Merck (India) Limited, Mumbai.
6. Eppendorff tubes (2 ml): Tarsons Products Pvt. Ltd., Kolkata.
7. Centrifuge tubes (15 ml): Tarsons Products Pvt. Ltd., Kolkata.
8. Micro tips (1 ml, 0.2 ml, and 10 µl): Tarsons Products Pvt. Ltd., Kolkata

Equipment

The HPLC system with LC-2010HT HPLC Spectrophotometer detector (Shimadzu, Kyoto, Japan). Synergi 4u Fusion-RP 80A, 5 μm , 250 \times 4.6 mm, SS C18 column (Denali) was used for the analysis.

Chromatographic conditions

Mobile phase : Acetonitrile: Acetate buffer (4.5) mixture (60:40)
 Flow rate : 1 ml/min
 Pressure : 100 kg.f/cm²
 Injection volume : 50 μl
 Column temperature : Room temperature
 UV detection at : 230 nm

Preparation of mobile phase

Mobile phase consisting of acetonitrile: Acetate buffer 4.5 (60:40) was prepared by addition of specified quantities and mixed thoroughly. Mobile phase was degassed and used for the HPLC analysis; 1.0 ml/min flow rate was maintained throughout the analysis. The eluent was monitored using UV detector set at 230 nm.

Preparation of standard solution

Stock solutions of 1 mg/ml of paclitaxel were prepared in double distilled water. These solutions were further diluted with double distilled water to produce working stock solutions of 100; 10 $\mu\text{g}/\text{ml}$. All solutions were stored at -4°C .

Preparation of ammonium acetate buffer (pH 4.5)

About 1.44 g of ammonium acetate was weighed accurately and dissolved in 1000 ml of Millipore water. The pH was adjusted using glacial acetic acid.

Extraction procedure

The extraction of paclitaxel from the biological matrix was carried out by using protein precipitation method. This method was carried out by using precipitating agent acetonitrile. One hundred microliters of paclitaxel containing human plasma sample was taken into 1.5 ml of centrifuge tubes and 10 μl of 100 $\mu\text{g}/\text{ml}$ celecoxib was added as internal standard and vortexed for 5 min, then it was centrifuged at 10,000 rpm for 10 min, and the clear supernatant (around 50 μl each) was transferred into HPLC vials and was subjected to HPLC analysis.

Preparation of calibration curve of paclitaxel in human plasma

Plasma used for plotting the standard graph was obtained from healthy volunteers. Different concentrations (50,100, 200, 500, 1000, 2500, 5000, and 10,000 ng/ml) of paclitaxel along with a constant concentration of internal standard (100 $\mu\text{g}/\text{ml}$) in plasma were prepared for calibration curve. The samples were treated as above for extraction. The extracted sample (50 μl) was injected and eluted with mobile phase. Column solvents were degassed before use. The peak ratios of responses of standard drug (paclitaxel) and internal standard (celecoxib 100 μg) were noted down. The peak ratios of responses multiplied by 1000, obtained at different concentrations of the drug, were plotted against the concentrations of drug. The slope of the plot determined by the method of least square regression analysis was used to calculate the paclitaxel concentration in the unknown sample [Table 1]. The linearity was found to be in the range 50–10,000 ng/ml of paclitaxel in plasma, with a mean regression correlation coefficient of ($r^2 = 0.9996$) in plasma matrix [Figure 1]. The lowest limit of quantification was established at 50 ng/ml and the upper limit of quantification at 10,000 ng/ml, both the mean percentage deviation and the between run precision were less than 5%. The retention times of paclitaxel and celecoxib were 6.7 and 10.6 min, respectively.

Analysis of the blood samples

Blood samples were run along with quality controls, and concentrations were determined from calibration curve. The pharmacokinetic parameters were estimated with manual calculators using the following equations.^[8]

1. Total clearance:
 $\text{Clearance} = \text{dosing rate}/C_{\text{ss}}$ (peak plasma concentration at steady state); units = l/h
2. Volume of distribution:

Table 1: Linearity of paclitaxel and internal standard at various concentrations

Drug concentrations (ng/ml)	Drug response	Internal standard	Peak ratio
50	3,923	235,089	0.01
100	8,874	229,044	0.04
200	23,504	231,579	0.10
500	43,517	247,732	0.18
1,000	95,886	226,548	0.42
2,500	216,643	236,578	0.92
5,000	435,636	221,545	1.96
10,000	895,955	225,074	3.85

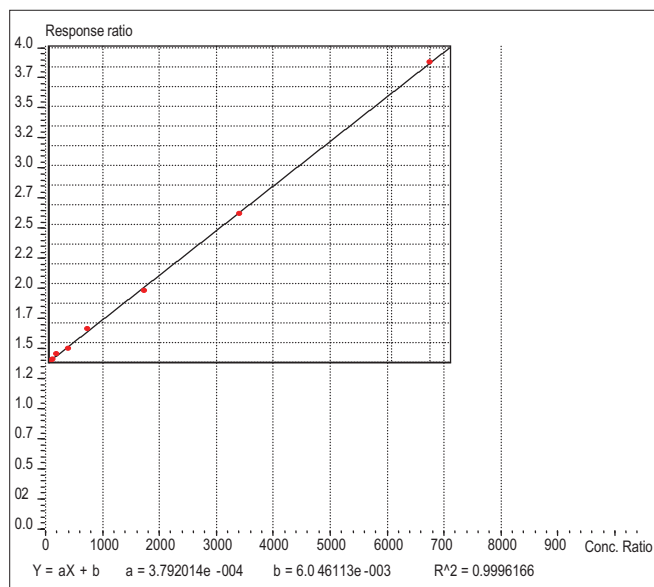


Figure 1: Linearity plot of paclitaxel

Volume of distribution

$$= \frac{\text{amount present in the body}}{C_{ss} \text{ (peak plasma concentration at steady state)}}; \text{ units} = 1$$

3. Elimination rate constant:
Elimination rate constant = clearance/volume of distribution; units = min^{-1}
4. Half-life:
Half-life ($t_{1/2}$) = $0.693/K$; units = hour or min.
5. Area under curve:
Area under curve = clearance/volume of distribution; units = mg/ml.
6. Mean residence time (MRT):
MRT = volume of distribution/clearance; units = h

RESULTS

A total of 23 cancer patients (8 males and 15 females) were enrolled in this study. The baseline characteristics of the study population are shown in Table 2. The mean age of the patients was 47 years (range 28–71 years) and the mean body surface area was 1.54 m^2 (range $1.28\text{--}1.94 \text{ m}^2$). Majority of the patients ($n=10$; 43.48%) had breast cancer.

Estimation of plasma concentration of paclitaxel

The study adopted a validated HPLC assay for the determination of the concentration of paclitaxel in plasma. The blank, standard, and test chromatograms (plasma) are shown in Figures 2 and 3. Paclitaxel was given as a constant

Table 2: Baseline characteristics of study population

Patient characteristics ($n=23$)	Mean (%)	Range
Males/females	8/15	—
Age (years)	47	28–71
Body surface area (m^2)	1.54	1.28–1.94
Body weight (kg)	57	40–77
Serum creatinine (mg/dl)	0.85	0.4–1.3
Dose (mg)	205	130–260
Cancer type		
Breast	10 (43.47)	
Stomach	3 (13.04)	
Lung	1 (3.85)	
Ovarian	3 (13.04)	
Esophagus	1 (3.85)	
Pancreas	1 (3.85)	
Nasopharyngeal	2 (8.7)	
Cervix	2 (8.7)	

rate intravenous infusion for 3 h only and then stopped; hence peak concentration and steady state were achieved at 3 h and subsequently dropped.

Pharmacokinetic parameters

The pharmacokinetic parameters of different doses of paclitaxel in the study population are shown in Table 3. The overall mean clearance was found to be $47.5847 \pm 142.0281/\text{h}$; the mean volume of distribution was $142.028 \pm 73.438 \text{ l}$; mean elimination rate constant was $0.336 \pm 0.002/\text{hour}$; mean half-life was $2.086 \pm 0.009 \text{ h}$; mean area under the curve (AUC) was $5.5917 \pm 2.707 \text{ mg/ml}\cdot\text{h}$; the mean of MRT was $2.980 \pm 0.0131 \text{ h}$. The mean values of the pharmacokinetic parameters (clearance, volume of distribution, elimination rate constant, half-life, AUC, and MRT) for doses of paclitaxel at 130, 230, 200, and 260 mg of constant infusion for 3 h were given as in Table 3.

Statistical analysis

The results were statistically analyzed by analysis of variance (ANOVA). The age of the patients was correlated with mean volume of distribution [Table 4]. The volume of distribution decreased with increase in age but was not statistically significant ($F=0.09$; $P=0.914$). There was a significant increase in volume of distribution as body weight increased ($F=1.103$; $P=0.351$) as shown in Table 5. The body surface area ($F=0.332$; $P=0.802$ and serum creatinine levels ($F=0.08$; $P=0.780$) did not have a significant effect on mean volume of distribution, and the patients with serum creatinine values >1.0 showed an increased volume of distribution [Tables 6 and 7]. Clearance was directly proportional to volume of distribution ($F=1.22$; $P=1.89$) but was not statistically significant [Table 8].

Table 3: Mean values of paclitaxel pharmacokinetic parameters at different doses

Dose (mg/m ²)	No. of patients (N=23)	Mean C _{ss} (mg)	Mean CL (l/h)	Mean Vd (l)	Mean K (1/h)	Mean T _{1/2} (h)	Mean AUC (mg/ml.h)	Mean MRT (h)
130	5	0.003	8.56	54.84	0.34	2.09	8.52	2.95
200	6	0.002	34.65	103.44	0.34	2.09	6.17	2.99
230	3	0.001	54.73	163.48	0.34	2.09	4.33	2.99
260	9	0.001	69.95	209.04	0.34	2.09	3.99	2.99
		Mean	47.58	142.03	0.34	2.09	5.59	2.98
		SD	24.52	73.44	0.00	0.00	2.71	0.014

Table 4: Age versus mean volume of distribution

Age (years) (n=23)	Mean Vd (l)	Standard deviation	ANOVA
<40 (n=6)	153	±81.04	F=0.09
40-60 (n=16)	138	±75.16	P=0.914
>60 (n=1)	132	±73.43	

Table 5: Weight versus mean volume of distribution

Weight (kg) (n=23)	Mean Vd (l)	Standard deviation	ANOVA
40-50 (n=6)	105	±47.17	F=1.103
50-60 (n=9)	147	±99.65	P=0.351*
>60 (n=8)	163	±48.24	

*Significant.

Table 6: Body surface area versus mean volume of distribution

Body surface area (m ²) (N=23)	Mean Vd (l)	Standard deviation	ANOVA
1.2-1.4 (n=6)	133	±61.1	F=0.332
>1.4-1.6 (n=8)	129	±87.9	P=0.802
>1.6-1.8 (n=8)	163	±75.5	
>1.8-2 (n=1)	118	±73.4	

Table 7: Serum creatinine versus mean volume of distribution

Serum creatinine (mg/dl) (N=23)	Mean Vd (l)	Standard deviation	ANOVA
<1.2 (n=17)	130	±71.89	F=0.080
>1.2 (n=6)	173	±74.64	P=0.780

Table 8: Clearance versus mean volume of distribution

Clearance (Liters/Hour) (N=23)	Mean Vd (l)	Standard deviation	ANOVA
<40 (n=10)	76	±35.00	F=1.22
40-60 (n=4)	125	±5.04	P=1.89
>60 (n=9)	221	±29.07	

DISCUSSION

Paclitaxel is a promising drug in the treatment of different solid tumors. In our hospital, 3-h infusion is used at four dose levels 130, 200, 230, and 260 mg. This study was undertaken with the aim of assessing pharmacokinetic parameters in constant rate intravenous infusion model at different dose levels. Several studies have shown that

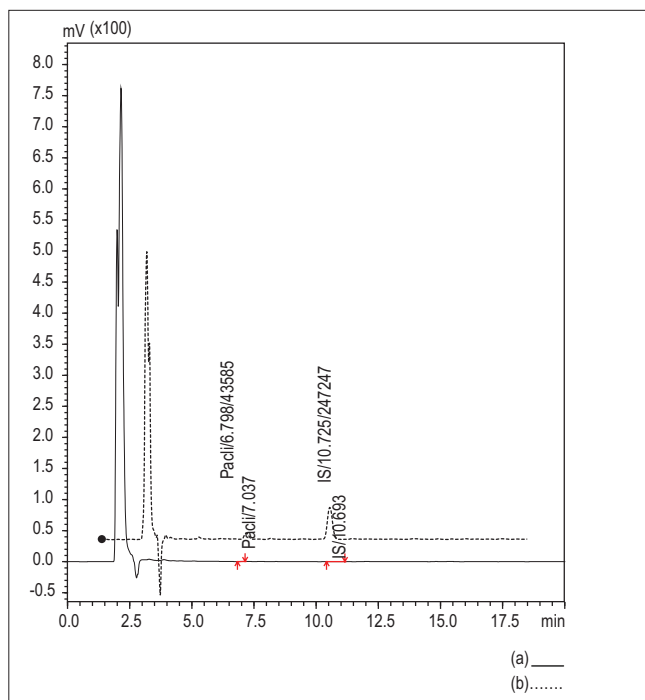


Figure 2: HPLC Chromatograms (a) chromatogram of standards; (b) chromatogram of human plasma (healthy volunteers)

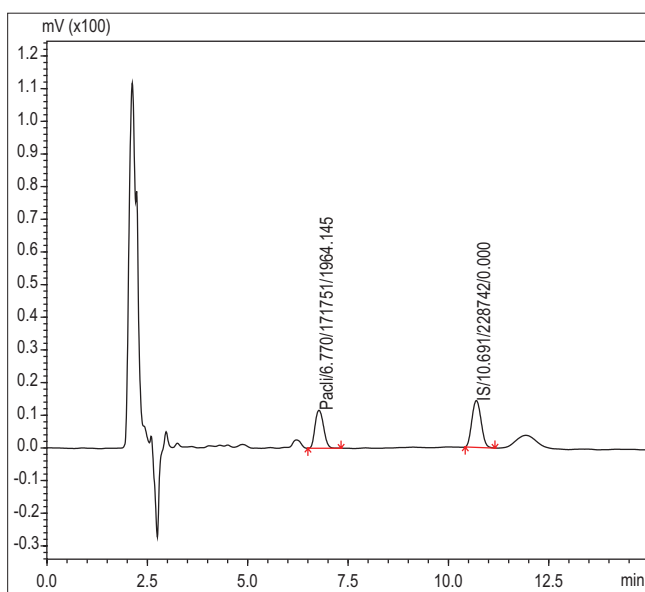


Figure 3: HPLC chromatogram patients' blood samples at 3 h

paclitaxel shows nonlinear pharmacokinetics with saturable distribution and saturable elimination.^[1,9]

The nonlinear pharmacokinetic behavior of paclitaxel in patients has now been well established. Both an over proportional increase in C_{max} and a reduction in the Cl were found upon dosage escalation. Although this nonlinearity appears to occur with all administration schedules, it is more profound when the drug is administered within a short period of time (e.g., 3 h), rather than by a lasting infusion (24 or 96 h). These findings were thought to be consistent with saturable processes of elimination and distribution of paclitaxel, occurring when the plasma concentration of the drug is above a “saturation point.” A greater than proportional increase in the area under the AUC₂ and the peak plasma level (C_{max}) with dosage suggests that both the elimination and the tissue distribution are saturable processes.^[14,15]

Paclitaxel pharmacokinetics at different dose levels and different duration of infusions has been documented in several studies. Studies have reported that pharmacokinetic parameters such as AUC, C_{max} , and clearance were not found to be different at different dose levels, indicating the nonlinear pharmacokinetic behavior.^[16] Similarly, the difference in pharmacokinetic parameters of paclitaxel (Cl , V_d , and AUC) at four dose levels were not statistically significant in this study.

In this study, the pharmacokinetic data have shown a system of saturable elimination; that is low plasma concentrations are cleared faster than high concentrations. This indicates nonlinear pharmacokinetics. Two patients at the dose of 260 mg have shown low steady state (C_{ss}) concentrations (0.00097 and 0.00220) indicating larger clearances (89.6 and 39.5 l/h, respectively).^[9] The average peak plasma concentration achieved in patients receiving 130 mg dosage was 2 $\mu\text{g/ml}$ which was similar to that quoted in the literature; but an increase in the dose was not associated with increased peak plasma concentrations. Elimination half-life ($t_{1/2}$) of paclitaxel was found to be 2.09 h, which is the same as quoted in the literature (2.33 h).^[17,18]

In a study by Mross on the pharmacokinetics of 3-h paclitaxel infusion, the volume of distribution at steady state (V_{ss}) was found to be 138 l/m², while in our study the value was 142 l/m². This indicates a wide distribution of paclitaxel in body fluids and tissues and nearly 85% bound to plasma proteins.^[8] The elimination rate constant calculated from the equation $k = cl/v$ (0.33) and from semi log graph (0.34) have shown similar values.

Peripheral neuropathy was the only adverse effect reported by most of the patients in this study. Other side effects such as hypotension, congestive heart failure, and bradycardia were not reported. Having assessed the pharmacokinetic parameters of paclitaxel, we can optimize the dose to achieve the desired plasma drug concentration to maximize the response and reduce the toxicity of the drug.

The pharmacokinetics of paclitaxel (Pacliron) in patients with different types of solid tumor has been evaluated. Four fixed doses have been used 130, 200, 230, and 260 mg/m². The regimens were well tolerated by the patients.

This study is limited by the fact that the sample size was small, and the blood samples were difficult to collect at the post infusion period; however, we were able to collect blood samples at 0, 1, and 3rd h for 23 patients and post infusion samples for five patients at 5th hour and 13th hour.

CONCLUSION

Clinical pharmacokinetics is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient. Primary goals of clinical pharmacokinetics include enhancing efficacy and decreasing toxicity of a patient's drug therapy. The development of strong correlations between drug concentrations and their pharmacologic responses has enabled clinicians to apply pharmacokinetic principles to actual patient situations. To administer drugs optimally we need the knowledge of mechanism of drug absorption and also its kinetics.

In this study, paclitaxel has shown nonlinear pharmacokinetics, but the peak plasma concentrations did not increase with the dose. Further studies are required to correlate serious toxic symptoms such as myelosuppression with dose intensity.

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