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Pharmacokinetics of Pentobarbital After Intravenous and Oral Administration[1]

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The plasma levels in humans of pentobarbital were determined after intravenous administration of a 50 mg dose. It was found that pentobarbital is distributed in at least two kinetically distinct body compartments: a central, or "serum," compartment and a peripheral, or "tissue," compartment. By use of established mathematical techniques, values were assigned to the rate constants controlling the distribution and overall elimination of the drug from the body. The oral absorption of pentobarbital in fasted and nonfasted subjects was determined by mathematical analysis of the plasma level data following oral administration of a 50 mg dose. It was found that the presence of food significantly reduces the apparent absorption rate constant but not the amount absorbed. The absorption of a second dose, given 1.5 hr after the first dose, in nonfasted subjects was not affected, and a rapid increase in plasma levels occurred after this administration.

KEY WORDS: absorption kinetics; oral pentobarbital; effect of food on oral absorption of pentobarbital in humans; pentobarbital pharmacokinetics; intravenous and oral administration; effect of food on barbiturate absorption in humans.

INTRODUCTION

Even though pentobarbital is a drug that has been in use for many years, its pharmacokinetics have not been well defined. Early work by Brodie *et al.* (1) gave the blood levels of pentobarbital in man after intravenous administration of large doses (750 mg to 1 g), and Riegelman *et al.* (2) later applied a two-compartment open kinetic model to these data. Improvements in the sensitivity of the assay for pentobarbital now make it feasible to determine the pharmacokinetics after administration of a therapeutic

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dose. Determination of the kinetic model also allows one to study the influence of physiological conditions and states on the parameters of the model. One example is the influence of food on the oral absorption of the drug.

It has long been recognized that the presence of food in the gastrointestinal tract with orally administered drug products may significantly influence the rate of drug absorption and/or the total amount of the drug absorbed. Several reports have appeared which show that administration of certain drug products, e.g., griseofulvin, with oils or fatty meals greatly increased their absorption (3–5). More commonly, however, the presence of food decreases the oral absorption of drugs (6–8). In most of these cases, the reduction in serum or plasma levels was associated with a reduction in both the rate of drug absorption and the total amount of drug absorbed. In other cases, however, only the rate of absorption seems to have been reduced. For example, MacDonald *et al.* (9) showed that the oral absorption of four sulfonamides was delayed but the amount absorbed was not reduced in nonfasted subjects. The effect of food on barbiturate absorption after oral administration is of particular interest since these drugs are in widespread use as sedatives and hypnotics in situations where food consumption is not controlled.

There have been a number of investigations concerned with the oral absorption characteristics of barbiturates. For example, Kakemi *et al.* (10, 11) studied the effect of *p*H on the *in situ* absorption of various barbiturates from rat stomach and intestine. Sjegren *et al.* (12) studied absorption of barbiturates from various oral dosage forms, and Hume *et al.* (13) studied the serum level profiles for ultra-short-acting barbiturates following oral administration to man. Even though many of the factors affecting oral absorption of barbiturates have been characterized, little work has been done on the effect of food.

A report by Hume *et al.* (13) and preliminary work in our laboratories (14) suggest that delayed but complete absorption probably occurs following oral administration of sedative-hypnotic barbiturates with food. The clinical significance of this phenomenon with the barbiturates is illustrated by the fact that in the study conducted by Hume *et al.* (13) a subject who consumed a single cheese sandwich before the oral administration of 10 μg/kg of thiopental exhibited delayed but greatly prolonged sleep as well as delayed but prolonged drug blood levels apparently due to the delayed but complete absorption of the drug. The work in our laboratory also showed that food greatly influenced the pharmacological action of phenobarbital. Fasted rats given a 100 mg/kg dose of phenobarbital had an average sleeping time of 227 min; however, the same dose in nonfasted rats produced no hypnotic effect in any of the rats.

It was the purpose of the present investigation to determine a pharmacokinetic model for the absorption, distribution, and elimination of pentobarbital in humans and to determine the influence of food on the blood levels and the absorption parameter of the model.

MATERIALS AND METHODS

The following drug products were used: pentobarbital sodium capsules,[3] 50 mg of sodium pentobarbital; pentobarbital sodium for injection,[4] 50 mg/ml sodium pentobarbital; mephobarbital N.F. XII. All chemicals used in the study were reagent grade.

Selection of Subjects

Five healthy male volunteers aged 21 or over ranging in weight from 69.0 to 89.5 kg were selected for the study. These volunteers had not consumed any drug substances for at least 1 week prior to pentobarbital administration. These subjects participated in three studies with each study day separated by at least 2 weeks. Each study was begun in the early morning following an overnight fast. On study day 1, each subject received 50 mg of sodium pentobarbital intravenously by 5 min zero-order infusion. Experimental timing was begun exactly in the middle of the infusion period. On study day 2, each subject received a single oral capsule containing 50 mg of sodium pentobarbital. On study day 3, each subject ate a standard meal consisting of 30 g oatmeal (by weight), 60 ml milk, and 210 ml coffee (brewed) with 10 g of sugar. Fifteen minutes after the meal, each subject received a single oral capsule containing 50 mg of sodium pentobarbital and then a second capsule 1.5 hr after receiving the first capsule. In the intravenous study, the subjects were allowed black coffee and water *ad libitum*. On study days 2 and 3, no food or water was allowed until the third experimental hour.

Plasma Specimen Collections

On study day 1, specimens were collected by means of an indwelling venous catheter at 5, 10, 20, 30, and 45 min and at 1.0, 1.5, and 2.0 hr after administration. Thereafter, the specimens were collected by serial venous puncture at 3, 4, 5, 12, 24, 35, 48, and 60 hr after administration.

On Study day 2, specimens were collected at 0.5, 1.0, 1.5, 2.5, 3.0, 4.0, 6.0, and 7.0 hr after administration of the first capsule.

[3]Nembutal Sodium (Lot No. 119408), Abbott Laboratories.
[4]Nembutal Sodium for Injection (Lot No. 3778), Abbott Laboratories.

After collection in heparinized Vacutainer tubes, the specimens were centrifuged and the plasma was separated and frozen until assayed.

Assay of Pentobarbital in Plasma

To 1.0 ml of plasma in a 15 ml screw-top tube was added 1.0 ml of a 2.0 μg/ml solution of mephobarbital in water as the internal standard and 0.5 ml of 1 *N* HCl. The mixture was extracted with two 5 ml portions of ether by mixing on a Vortex mixer for 1 min. The combined extract was then washed with 2.0 ml of a 3 % (w/w) solution of sodium bicarbonate by shaking for 30 sec on the Vortex mixer. The ether layer was separated and evaporated in a water bath at 40°C to a volume of 0.1 and 0.2 ml, and 0.2 μl was injected into a gas chromatograph.

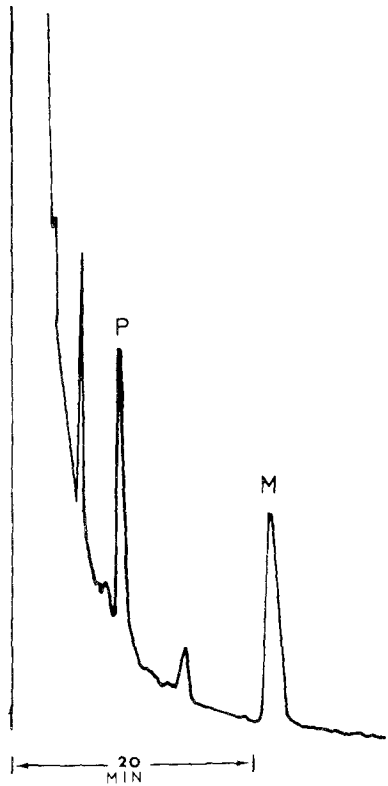

Fig. 1. Typical gas chromatogram of pentobarbital (P) with mephobarbital (M) as the internal standard (see text).

A Varian-Aerograph Series 2700 gas chromatograph equipped with a hydrogen flame ionization detector was used. The column was 6 ft by $\frac{1}{4}$ inch (OD) glass containing a packing of 3% OV-17 on chromosorb G HP (AW-DMCS), 100/120 mesh (Applied Science Laboratories). The column conditions were column temperature, 190°C; injector temperature, 240°C; detector temperature, 240°C; N_2 and H_2 flow rates, 30 ml/min; air flow rate, 300 ml/min. The retention time for pentobarbital under these conditions is 10 min, and for mephobarbital it is 18.5 min. The calibration curve for pentobarbital was obtained by plotting the concentration of pentobarbital against the peak area ratio of pentobarbital to mephobarbital. The standard samples were prepared by dissolving known amounts of pentobarbital and marker in plasma and then using the extraction procedure described above. Preliminary studies indicated that frozen specimens were stable for at least two months. All specimens were analyzed within 2 weeks. A typical chromatogram is shown in Fig. 1 using the above procedure.

RESULTS AND DISCUSSION

Five subject mean plasma levels of pentobarbital following intravenous administration of 50 mg of sodium pentobarbital are shown in Table I and Fig. 2. These results show that the distribution phase (α-phase) of pentobarbital was approximately 4 hr and that elimination occurred with a

Table I. Plasma Levels of Pentobarbital (μg/ml) After Intravenous Administration of 50 mg by 5 min Infusion

	Subject					
Time (hr)	L.N.	R.M.	G.B.	B.G.	R.B.	Mean ± SD
0.08	1.26	1.33	1.18	1.05	1.06	1.18 ± 0.12
0.17	1.15	0.99	0.92	0.92	0.93	0.98 ± 0.10
0.33	0.95	0.94	0.70	0.84	0.77	0.84 ± 0.11
0.50	0.78	0.91	—	−0.60	0.71	0.75 ± 0.12
0.75	0.56	0.87	—	0.46	0.63	0.63 ± 0.15
1.00	0.52	0.73	0.44	0.41	0.60	0.54 ± 0.11
1.50	0.48	0.48	0.36	0.39	0.56	0.45 ± 0.08
2.00	0.40	0.56	0.33	0.38	0.45	0.42 ± 0.08
3.00	0.39	0.50	—	0.35	0.51	0.43 ± 0.08
4.00	0.38	0.49	0.32	0.31	0.35	0.37 ± 0.07
6.00	0.36	0.47	0.27	0.34	0.31	0.35 ± 0.08
12.0	0.34	0.38	0.26	0.27	0.30	0.31 ± 0.05
24.0	0.32	0.35	0.24	0.22	0.24	0.27 ± 0.06
36.0	0.25	0.28	0.22	0.24	0.20	0.24 ± 0.03
48.0	0.23	0.23	0.19	0.23	0.17	0.21 ± 0.03
60.0	—	0.19	0.18	0.20	0.17	0.19 ± 0.02

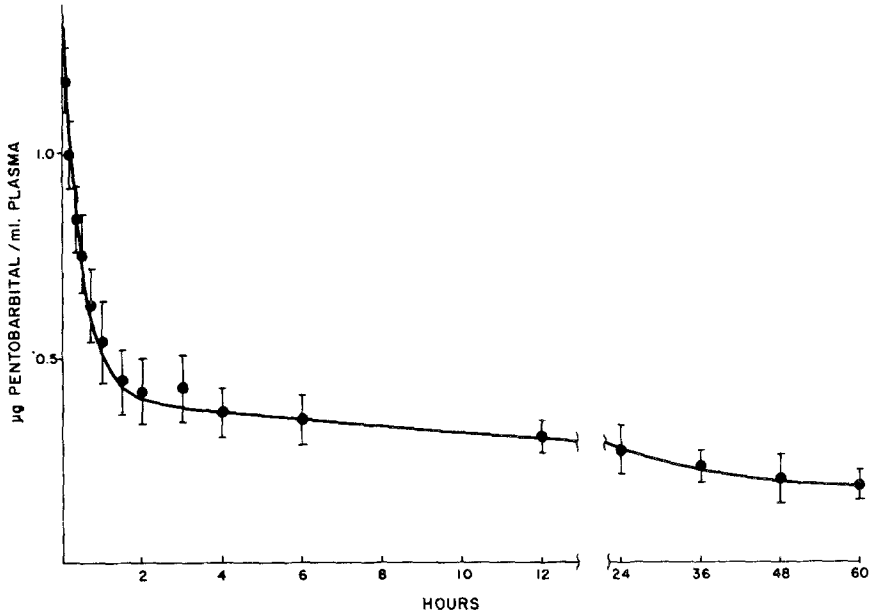

Fig. 2. Five subject mean (±SD) plasma levels of pentobarbital following intravenous administration of 50 mg.

harmonic mean β-phase half-life of about 50 hr. This behavior suggests that for pentobarbital the body consists of two or more kinetically distinct compartments: a central plasma compartment and one or more extravascular compartments.

The plasma curve for pentobarbital may be represented mathematically as a sum of exponentials

$$C_p = \Sigma A_i e^{-\alpha_i t}$$

where A_i's are constants, α_i's are complex rate constants, and C_p is the concentration of pentobarbital in plasma at time t. The A_i's, α_i's, and number of exponentials needed can be determined by the method of residuals (15). When this was done, it was found that the plasma curve could be described by a two-term exponential equation. The estimates for A_i's and α_i's were used to calculate the rate constants for the following model (equation 1) for each individual:

Two-compartment open model

$$\text{Drug in blood} \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} \text{Drug in tissues} \qquad (1)$$

$$\Big\downarrow k_{el}$$

Drug eliminated

Table II. Two-Compartment Open Model Parameters for Five Subjects (by SAAM 23)[a]

Subject	S.S.	k_{el} (hr^{-1})	k_{21} (hr^{-1})	k_{12} (hr^{-1})	Vp (l)
L.N.	0.004	0.043	0.599	1.524	34
R.M.	0.017	0.041	0.573	0.860	42
G.B.	0.003	0.036	0.508	1.405	39
B.G.	0.012	0.033	0.614	1.568	45
R.B.	0.011	0.036	0.281	0.455	46
Mean ± SD		0.038 ± 0.004	0.515 ± 0.137	1.162 ± 0.486	41 ± 4.8

[a]Initial estimates of k_{el}, k_{21}, and k_{12} were 0.040, 0.509, and 1.080, respectively.

The average rate constants determined in this manner were used as initial estimates in the SAAM 23 digital computer program (16) to determine best fits by regression. The initial estimates used and the rate constants determined by the program are shown in Table II. The results of the computations show that the two-compartment open model constants had small individual variances and were not much different from the initial estimates. From these results, it was concluded that the two-compartment open model adequately describes the kinetics of pentobarbital in humans. Figure 2 illustrates the agreement between the mean plasma levels and this model. The line in Fig. 2 was drawn by an analog computer programmed with the two-compartment open model and the mean rate constant from Table II. The good agreement indicated that averaging rate constants is about the same as averaging plasma levels in this case. It should be noted that Riegelman *et al.* (2) had previously suggested a two-compartment open model to describe pentobarbital kinetics employing data reported by Brodie *et al.* (1), and their results were similar to those obtained here. However, their volume of the plasma compartment was considerably larger, and this difference may be due to dose-dependent kinetics since the dose employed was 20 times the dose in this study. As a consequence of these results, the two-compartment open model was used in the analysis of the oral absorption data.

Individual plasma levels following oral administration of a 50 mg capsule (subjects fasted) are shown in Table III. The absorption rate constant (k_a) was calculated for each subject using his own rate constants from the intravenous study according to the method of Loo and Riegelman (17). Rate constants and lag times were determined by examination of plots of amount unabsorbed *vs.* time (18). The individual and average k_a's and apparent lag times are shown in Table III. The amount of pentobarbital remaining unabsorbed as calculated by the Loo–Riegelman method showed that 98.5 ± 8.4 (SD)% of the oral dose of pentobarbital was absorbed.

Figure 3 shows five subject mean (±SD) plasma levels of pentobarbital following oral administration of 50 mg of sodium pentobarbital to fasting

Table III. Plasma Levels of Pentobarbital (μg/ml) After Administration of a Single 50 mg Oral Capsule to Fasted Subjects

	Subject					
Time (hr)	L.N.	R.M.	G.B.	B.G.	R.B.	Mean ± SD
0.5	0.280	0.582	0.435	0.380	0.354	0.406 ± 0.10
1.0	0.615	0.831	0.630	0.880	0.700	0.731 ± 0.11
1.5	0.650	0.650	0.480	0.680	0.510	0.594 ± 0.09
2.0	0.530	0.580	0.420	0.605	0.400	0.507 ± 0.09
3.0	0.382	0.560	0.480	0.500	0.305	0.445 ± 0.09
4.0	0.365	0.345	0.435	0.415	0.230	0.358 ± 0.08
5.0	0.352	0.347	0.387	0.375	0.300	0.352 ± 0.03
6.0	0.314	0.240	0.330	0.350	0.280	0.302 ± 0.03
k_a (hr^{-1})	1.87	1.82	1.71	2.57	2.00	2.00 ± 0.34
Lag time (hr)	0.40	0.30	0.15	0.35	0.32	0.30 ± 0.09

subjects. The line in Fig. 3 was drawn by an analog computer programmed with the average k_a and lag time from Table III. From the analog fit of the data, it was apparent that the model adequately described oral pentobarbital absorption when subjects were fasted. It should be noted that only a few points could be used in calculating k_a and that the analog computer fit was important in demonstrating that the rate and extent of absorption were consistent with the plasma profile observed following oral administration.

Individual plasma levels of pentobarbital following oral administration of a 50 mg capsule 15 min after a light breakfast followed by a second 50 mg capsule 1.5 hr after the first capsule are shown in Table IV. Five subject average (±SD) plasma levels of pentobarbital for this study are

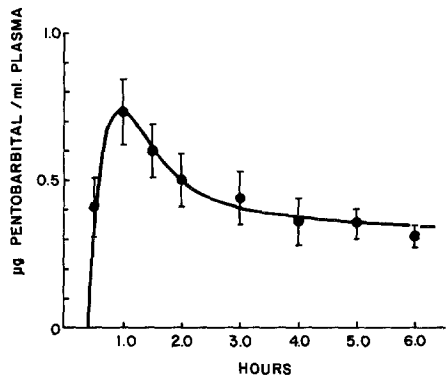

Fig. 3. Five subject mean (±SD) plasma levels of pentobarbital following oral administration of 50 mg to fasted subjects.

Table IV. Plasma Levels of Pentobarbital (μg/ml) in Nonfasted Subjects Given Two 50 mg Doses 1.5 hr Apart

	Subject					
Time (hr)	L.N.	R.M.	G.B.	B.G.	R.B.	Mean $\pm$ SD
0.5	0.103	0.156	0.371	0.162	0.157	0.190 $\pm$ 0.100
1.0	0.312	0.421	0.667	0.356	0.294	0.410 $\pm$ 0.150
1.5	0.581	0.470	0.681	0.439	0.548	0.544 $\pm$ 0.096
2.0	1.040	1.150	0.865	1.200	0.899	1.031 $\pm$ 0.148
2.5	1.168	1.120	1.130	1.145	1.150	1.143 $\pm$ 0.020
3.0	1.260	1.078	1.150	1.182	1.030	1.140 $\pm$ 0.090
4.0	1.150	1.100	0.975	1.120	0.908	1.051 $\pm$ 0.104
5.0	1.115	0.956	0.645	0.900	0.888	0.901 $\pm$ 0.170
6.0	1.095	0.859	0.750	0.740	0.860	0.861 $\pm$ 0.128
k'_a (hr^{-1})	0.631	0.928	0.771	0.559	0.693	0.716 $\pm$ 0.140
Lag time (hr)	0.40	0.25	0.33	0.30	0.20	0.30 $\pm$ 0.07

shown in Fig. 4. The apparent individual absorption rate constants (k'_a) for the first dose (15 min after breakfast) were calculated by the Loo–Riegalman method by assuming that 100% of the dose was eventually absorbed and applying the individual parameters from Table II. The apparent rate constants (k'_a) shown in Table IV are significantly less ($p < 0.005$ using the T test for difference of means) than the k_a's given in Table III. Thus the presence of a relatively small amount of food in the stomach at the time an oral dose of sodium pentobarbital is administered significantly slows the rate of pentobarbital appearance in the blood.

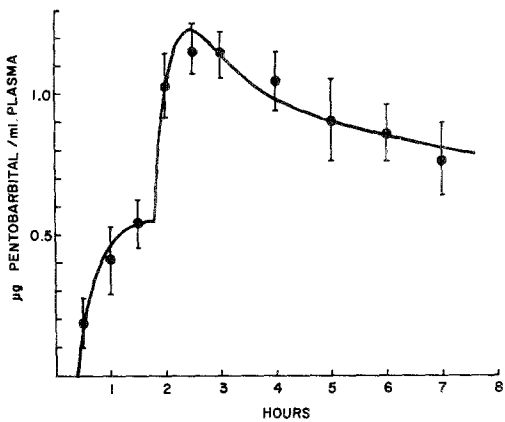

Fig. 4. Five subject mean ($\pm$SD) plasma levels of pentobarbital following oral administration of a 50 mg dose at time zero and a second 50 mg dose 1.5 hr later to nonfasted subjects.

An analog computer was used to draw the line in Fig. 4 and to determine the absorption behavior of the second dose in nonfasted subjects. It was found that when the computer was programmed with the average model parameters from Table II, with the average lag time and k_a' from Table IV for the first dose, and with the average k_a from Table III for the second dose, the solid line shown in Fig. 4 resulted. It was also assumed (from comparing the area under the curve with the area under the curve after intravenous administration) that 100% of each dose was absorbed.

In a recent paper by the authors (14) the effect of food on phenobarbital absorption in the rat was reported. In that work, it was found that the presence of food in the gastrointestinal tract decreased the rate of absorption but did not decrease the amount of phenobarbital ultimately absorbed. It was also found that, if a dosage regimen similar to that in the repeated dosing study of this investigation was used, the absorption rate of the first dose was decreased but the absorption of the second dose was rapid, with a concomitant rapid increase in plasma levels of phenobarbital.

The pharmacological action of phenobarbital, as measured by sleeping time, was later in the presence of food with the above dosage regimen. It was found that the onset of action was delayed and the duration greatly increased when food was present as compared to the effect when the rats were fasted.

It was concluded in that study that the primary effect of food on phenobarbital absorption was due to delayed gastric emptying, since barbiturates are poorly absorbed in the stomach and rapidly absorbed in the intestines, as shown by Kakemi *et al.* (10,11) and work in our laboratories (14).

The results of the present study indicate that the presence of food affects the absorption of pentobarbital in humans in a manner similar to its effect on phenobarbital absorption in rats. The results suggest the following: (a) The presence of food in the gastrointestinal tract slows the rate of absorption of pentobarbital but does not decrease the total amount absorbed. (b) If it is assumed that the stomach was cleared of food by the time of the administration of the second pentobarbital dose, it can be concluded that only food in the stomach affects the absorption of pentobarbital and that the mechanism producing the delay is stomach emptying. (c) An intense, prolonged pharmacological response (perhaps toxicity) can be expected following the second dose of pentobarbital administered following a meal.

The effect of variable barbiturate absorption when food is present in the gastrointestinal tract is of particular clinical significance because these drugs are widely used as sedatives and hypnotics in situations where neither food nor drug consumption is controlled. Our preliminary study in rats and the present investigation indicate that barbiturate absorption was markedly slowed in the presence of food but that eventually the oral doses

were completely absorbed. This effect significantly lowered serum or plasma levels in rats and in man, and dramatically reduced the pharmacological activity of the drug in rats.

In spite of the fact that the serum or plasma levels and activities of the barbiturates in rats and humans were reduced in the presence of food, significant plasma levels of unmetabolized barbiturates were nonetheless observed in both experiments. These levels were such that a second dose administered 1 hr after the initial dose produced a dramatic rise in the serum levels, activities, and toxicities of the drugs due to the combined residual absorption of the initial dose and rapid absorption of the second dose. The significance of this effect is illustrated by the fact that 25% of the rats employed in the multiple phenobarbital dose (2 × 150 mg/kg) study in nonfasted rats died, and an exaggerated pharmacological response was noted in the remaining animals.

The results of the phenobarbital study (14) and the present investigation suggest that food may play a significant role in altering the pharmacological profile of orally administered barbiturates. Initially, the presence of food would delay absorption and reduce the response; subsequent doses might lead to an exaggerated response and perhaps even intoxication. For example, if a patient takes a dose of a barbiturate shortly after a meal and is not sedated in about an hour, he may be tempted to take additional dose(s) just as the first dose is being absorbed. The result would be a rapid rise in barbiturate serum levels and a significant danger of exaggerated response.

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