

STUDY OF ANAESTHETIC, PHYSIOLOGICAL AND BIOCHEMICAL EFFECTS OF KETAMINE COMBINATION WITH FENTANYL AND DIAZEPAM IN RABBITS

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ABSTRACT

The study was conducted at the animal house of the collage of Veterinary medicine university of Basrah, the objective of this study to know effect ketamine drug as anesthetic agent in rabbits and comparison between several types of general anesthetic systems in rabbits and study the combination with Diazepam and fentanyl , in this study used (32) adult domestic rabbits from both gender , the average of body weight (1000-1900) grams , the rout of administration by intramuscular , were divided equally and randomly into four groups (8) rabbit in each groups .We were studied the induction time, surgical anesthesia time and recovery time also we were studied some physiological parameter (heart rate, respiratory rate and body temperature), also we were recorded (Degree of Analgesia, Eyes Reflexes and Degree of Muscle Relaxation).We were recorded data of this parameter before I.M administration at (Zero) minute and after I.M administration depending the following time (5, 10, 20, 30, 40, 50, 60) minute, until response the rabbit to external stimuli.The biochemical test are (ASTand ALT).

INTRODUCTION

Rabbits are used widely in biomedical research and it has also gained increasing popularity among urban families as a domestic pet ,commonly and widely used injectable anesthesia in the field and experimental settings, their safe use scientists and Veterinarians require experience ,proper facilities , and accurate calculation of dose in order to prevent or minimize undesirable effects (1) . Inhalation anesthesia has gained wide acceptance as a method for providing moderate to long periods of anesthesia in man and many animal. The anatomical conformation of the oral cavity of rabbits impedes visualization of the larynx, intubation is difficult. Therefore, parenteral anesthetic are often preferred in this species (2) The important way of reducing animal suffering is the use of anesthesia and analgesic

treatment in conjunction with surgery and other painful procedures for scientific quality, anesthetic techniques need to be reliable and safe, and the effects of the anesthetic and analgesic compounds on the research animals must be well documented, this is important to consider when experiments are performed and data collected under anesthesia (3).

The aim of this study was conducted to study some of the variables Physiological and biochemical and effects of ketamine combination with diazepam and fentanyl in rabbits.

MATERIALS AND METHODS

This study was used as thirty two local breed rabbits of both sexes weighting about 1000-1900 gm and age (6-8 months) in this study, animals were taken up from the local market of the city of Basra. We were staying at the animal house in the College of Veterinary Medicine at the University of Basra and kept in iron cages. The animals food is a vegetable and water *Ad libitum* under the same laboratory environment for a period of two weeks for the purpose of adaptation were given Intertrim-480ws (Sulfadiazine and Trimethoprim water-soluble powder) with water (0.6 gm/L) as prophylactic treatment against coccidiosis and Introvit- A (0.25 gm/L).

they were divided randomly into equally four groups:-

Control group (Con) :- Eight rabbits were injected with normal saline 0.9% (1 ml/kg B.W) I.M.

Group Ketamine (Ket) :- Eight rabbits were injected with Ketamine HCl (50 mg/kg B.W) I.M.

Group Ketamine and Diazepam (Ket+Dia) :- Eight rabbits were injected with Ketamine HCl (35mg/kg B.W) and Diazepam (5mg/kg B.W) I.M.

Group Ketamine and Fentanyl (Ket+Fen) :- Eight rabbits were injected with Ketamine HCl (35mg/kg B.W) and Fentanyl (0.025 mg/kg B.W) I.M.

Physiological parameter

We recorded the heart rate (by using of stethoscope), respiratory rate (based on counting thoracic Movement) and body temperature (by using electron rectal thermometer), before and during induction, anesthesia and recovery period at zero time and (5,10,20,30,40,50,60) minute after intra-muscular injection of anesthetic agents.

We observed the animals accurately from the moment of anesthesia administration until the reflexes were disappeared to evaluate the induction type if it was smooth, shivering with struggling movements. The total anesthetic period between disappearance and reappearance of reflexes were recorded. The recovery was observed from the time of reappearance of the reflex until complete consciousness. Degree of analgesia (by pin - prick of rabbit Mild degree of the analgesia +, Moderate analgesia ++ and Deep analgesia +++). Degree of hind leg muscle tone (by flexion and extension of the limb of rabbit Minimal degree of the relaxation +, Moderate relaxation ++ and Marked relaxation +++). [2,4,5]. Eye Reflexes Corneal by touching it using finger, Palpebral by touching the medial canthus, Eye ball movement.

Biochemical parameter

The blood samples were collected via cardiac puncturing with 23 G needle at times 60 to study the (AST and ALT) Enzyme.

Statistical Analysis

The results of experiment were analyzed by univalent analysis of variance (ANOVA) by using computerized SPSS (Statistical Packages for the Social Sciences) V.21 program. $P < 0.05$ was considered to be the limit of significance. The data were expressed as mean \pm standard deviation (means). Least significant difference test (LSD) was used to test the difference between groups (6).

RESULTS

Evaluation Nature of Induction.

After injecting the drug in (Ket) group the animal is suffering from muscle tonic and the induction time is about (3.750) minute. In (Ket + Dia) group the animal characterized with smoothly induction as well as in (Ket + Fen) group were the same signs and the induction time is about (3.813) and (3.500) respectively. table (1).

Evaluation of Anesthesia Time.

In (ket) group, the modality of anesthesia caused nice analgesia with total unconsciousness but some reflexes were low level, the duration time was kept in (24.125) minute, while the duration time in (Ket + Fen) group (24.875) minute, it has significant difference which is longer duration time in (Ket + Dia) group (32) minute at $P < 0.05$ among other group of experiment table (1).

Evaluation Nature of Recovery.

The recovery time was smoothly in nature in all groups ,in (Ket) group the recovery time was (60.125) minute for full recovery , while the recovery time was (77.875) minute in (Ket + Dia) group , in (Ket + Fen) group the duration of recovery time is about (73.625) minute ,there is no significant different among all groups at recovery time at $P < 0.05$ table (1).

Table (1): The mean of induction,anesthesia and recovery time in groups (Ket), (Ket+Dia) and (Ket+Fen).

<i>Group</i>	<i>IND/min</i>	<i>ANA/min</i>	<i>REC/min</i>
<i>Ket</i>	A 3.750 ±0.707	A 24.125 ±2.949	A 60.125 ±4.764
<i>Ket + Dia</i>	A 3.813 ±0.799	A 32.000 ±2.329	A 77.875 ±5.817
<i>Ket + Fen</i>	A 3.500 ±0.654	B 24.875 ±3.720	A 73.625 ±3.622
<i>L.S.D</i>	0.00	3.250	13.500

IND=induction , ANE= anesthesia, REC= recovery ,min= minutes, Ket=ketamine , Dia = diazepam, Fen=fentanyl ,LSD = Least significant difference.

✱ The difference in small letter mean significant difference at the ($P < 0.05$) level between treated groups. Evaluation of Muscle Relaxation.

In all groups, the muscle relaxation was minimal degree started at 5 minute after I.M injection and continuous for 25 minute . In (Ket) group, the animal become on the lateral position and at 35 minute the animal converted to the sternal position . In (Ket + dia) , group the animal converted to sternal position at 45 minute, while the (Ket + Fen) groups converted to the sternal position at 40 minute .

Evaluation Of Corneal, Palpebral And Eye Ball.

The reflexes of the eyes (Eyelids and Corneal) were never disappeared in all the treatment groups , while it become nearly weak at 10-30 minute in (Ket) and (Ket + Fen) groups and

10-40 minute in (Ket + Dia) group. The size of pupil was mydriasis in all group at 2-3 minute after I.M injection and at 10 minute in all groups started the pupil miosis and decreased gradually at 40 minute, in all groups the pupil dilatation at 60 minute .

Evaluation of Ear Analgesia.

The analgesia of Ear in rabbits mild ear analgesia or no disappear in (Ket) group and in (Ket + Dia) and (Ket + Fen) groups the analgesia occurs at 5-20minute.

Evaluation Of Body Temperature.

The result show gradual decrease in body temperature in (Ket) and (ket+fen) groups after injecting the drugs I.M ,while the body temperature significant difference and drops sharply in (ket+Dia) group start from 30 min until 60 min table (2) .

Table (2): The mean of body temperature (c°) in groups(Con), (Ket), (Ket+Dia) and (Ket+Fen).

<i>time</i> <i>group</i>	<i>Zero/min</i>	<i>5/min</i>	<i>10/min</i>	<i>20/min</i>	<i>30/min</i>	<i>40/min</i>	<i>50/min</i>	<i>60/min</i>
<i>Con</i>	A a 38.825 ±0.465	A a 38.875 ±0.413	A a 38.800 ±0.362	A a 38.738 ±0.396	A a 38.755 ±0.328	A a 38.638 ±0.324	A a 38.675 ±0.286	A a 38.725 ±0.345
<i>Ket</i>	A b 39.125 ±0.175	A a 38.700 ±0.456	B a 38.438 ±0.785	B a 37.838 ±0.755	B a 37.150 ±1.392	B a 36.875 ±1.254	B b 36.775 ±1.426	B a 36.913 ±1.295
<i>Ket + Dia</i>	A a 39.013 ±0.299	B a 38.188 ±0.589	A a 37.975 ±0.651	B a 37.113 ±0.823	B a 36.350 ±0.936	B a 35.850 ±0.761	B b 35.500 ±0.723	B a 35.150 ±0.972
<i>Ket + Fen</i>	A a 39.213 ±0.387	A a 38.663 ±0.420	A a 38.325 ±0.399	B a 37.575 ±0.757	B a 37.025 ±0.909	B a 36.650 ±1.239	B b 36.325 ±1.339	B a 36.150 ±1.574
<i>L.S.D</i>	0.510	0.510	0.683	0.545	0.363	0.363	0.548	0.630

Con= control, Ket=ketamine , Dia = diazepam, Fen= fentanyl , min= minutes, LSD = Least significant difference.

✱ The difference in small letter mean significant difference at the ($P < 0.05$) level between treated groups.

✱ The difference in capital letters mean significant differences ($P < 0.05$) in the time.

Evaluation Of Respiratory Rate.

The result showed the respiratory rate mildly decrease at (5-20)minute and increase gradually to the normal range in (Ket),(Ket+Dia), while respiration drop sharply at (5-30)minute and increases gradually in (ket + fen) group. table (3).

Table (3): The mean of the respiratory rate (rate/minutes) in groups (Con), (Ket), (Ket+Dia) and (Ket+Fen).

<i>time</i> <i>group</i>	<i>Zero/min</i>	<i>5/min</i>	<i>10/min</i>	<i>20/min</i>	<i>30/min</i>	<i>40/min</i>	<i>50/min</i>	<i>60/min</i>
<i>Con</i>	A a 62.00 ±8.298	A a 64.250 ±9.632	A a 65.375 ±15.647	A a 67.508 ±16.265	A a 65.750 ±13.285	A a 66.625 ±13.595	A a 69.875 ±16.702	A a 68.250 ±16.051
<i>Ket</i>	A a 75.125 ±11.691	B a 41.125 ±6.512	B a 42.250 ±6.453	A a 48.125 ±9.372	A a 57.375 ±11.350	A a 66.000 ±12.224	A a 67.625 ±10.183	A a 71.625 ±6.277
<i>Ket + Dia</i>	A a 66.375 ±15.371	A a 43.625 ±11.134	A a 39.875 ±12.788	A a 39.125 ±9.187	A a 43.750 ±10.180	A a 47.875 ±8.951	A a 53.250 ±11.535	A a 56.000 ±10.690
<i>Ket + Fen</i>	A a 67.625 ±13.437	C b 26.875 ±3.399	C b 27.000 ±2.449	B b 29.750 ±3.955	A a 40.875 ±9.402	A a 50.750 ±6.819	A a 55.500 ±9.196	B a 56.750 ±5.599
<i>L.S.D</i>	6.075	7.925	8.025	5.525	5.525	5.652	6.075	5.625

Con= control, Ket=ketamine , Dia = diazepam, Fen= fentanyl , min= minutes, LSD = Least significant difference.

✱ The difference in small letter mean significant difference at the (P<0.05) level between treated groups.

✱ The difference in capital letters mean significant differences (P<0.05) in the time.

Evaluation Of The Heart Rate.

In group (Ket) the heart rate increased through (5-30) minute and after that decreased at 40 minutes and continue to 60 minute . The heart rate decreases mildly through (30-60) minute in (Ket+Dia) group ,.In (Ket-Fen) group, the heart rate increased gradually from 5 minutes to 60 minutes table (4) .

Table (4): The mean of the heart rate (beat/minute) in groups (Con), (Ket), (Ket+Dia) and (Ket+Fen).

<i>time</i> <i>group</i>	<i>Zero/min</i>	<i>5/min</i>	<i>10/min</i>	<i>20/min</i>	<i>30/min</i>	<i>40/min</i>	<i>50/min</i>	<i>60/min</i>
<i>Con</i>	A a 237.000 ±17.792	A a 234.000 ±18.913	A a 238.500 ±18.291	A a 236.875 ±20.531	A a 233.000 ±28.122	A a 232.125 ±30.577	A a 238.500 ±27.500	A a 243.250 ±22.166
<i>Ket</i>	B a 211.625 ±17.303	B b 256.375 ±13.479	A a 250.500 ±20.556	A a 240.500 ±16.062	B b 232.500 ±6.740	A a 223.375 ±17.638	A a 225.000 ±27.836	A a 218.500 ±29.832
<i>Ket + Dia</i>	C a 249.750 ±80.926	C a 250.750 51.224	A a 245.500 ±42.152	A a 235.250 ±39.495	A a 223.500 ±37.136	A a 223.250 ±36.815	A a 228.250 ±36.448	A a 226.500 ±35.046
<i>Ket + Fen</i>	C a 234.000 ±28.605	C a 259.000 ±30.650	A a 254.250 ±22.587	A a 256.500 ±22.239	A a 249.250 ±23.855	A a 242.750 ±29.353	A a 250.125 ±23.835	A a 257.000 ±26.489
<i>L.S.D</i>	18.675	21.275	15.500	14.825	16.150	14.825	17.725	15.500

Con= control, Ket=ketamine , Dia = diazepam , Tra = tramadol , Fen= fentanyl , min= minutes, LSD = Least significant difference.

- ✱ The difference in small letter mean significant difference at the (P<0.05) level between treated groups.
- ✱ The difference in capital letters mean significant differences (P<0.05) in the time.

Evaluation Of The Ast And Alt Enzymes

The results of (Ket) group showed no significant decrease in the value of the AST enzyme compared with (Con) group while (Ket+Fen) group showed mildly increase in AST level, while (Ket+Dia) group showed significant decrease in AST level compared with (Con) group. The results of (Ket) group showed no significant decrease in level of ALT enzyme as compared with (Con) group, while (Ket+Dia), and (Ket+Fen) groups showed significant decrease in the value of the ALT enzyme as compared with (Con) group see table (5).

Table (5): The mean of AST (IU/L)and ALT (IU/L)in groups (Con), (Ket), (Ket+Dia), and (Ket+Fen).

<i>Group</i>	<i>AST(10–80)IU/L</i>	<i>ALT(10–70)IU/L</i>
<i>Con</i>	A 61.763 ±20.234	C 62.188 ±15.520
<i>Ket</i>	B 54.850 ±17.201	B 57.900 ±18.090
<i>Ket + Dia</i>	A 43.063 ±25.586	A 43.550 ±26.210
<i>Ket + Fen</i>	C 63.050 ±19.378	D 45.638 ±20.117
<i>L.S.D</i>	19.937	21.312

ALT = Alanine aminotransferase , AST= Aspartate aminotransferase Con= control, Ket=ketamine , Dia = diazepam, Fen= fentanyl , min= minutes, LSD = Least significant difference.

✱The difference in capital letters mean significant differences (P<0.05).

DISCUSSION

The result of induction after I.M injection showed that the rabbits are suffering from muscle tonic and excitement in (Ket) group that agrees with [7;8;9] due to the ketamine produce tonic –clonic muscle activity without muscle relaxation of limb muscle ,minimize the difference between (Ket) , (Ket + Dia) , and (Ket + Fen) groups, the duration time of induction are(3.750±0.707),(3.814±0.799),and (3.500±0.654) respectively .Induction stages of anesthesia were generally smooth and duration did not different significantly among groups. The length of anesthesia time is good for (Ket + Dia) group, is about (32) minutes which is good for short surgical operation in rabbits when compared with the other groups of experiment, This result was in agreement with [10], but other experiments show no differences in time of anesthesia .

we found that recovery time in all group varies from one group to another, in (Ket) group the recovery was violent convulsions and increased tonic-clonic muscle activity in most species

of animals, these results are consistent with [8,9,11]. as we seen in our experiment . In (Ket+Dia) group, the recovery was good and these results are consistent with [33,34]who found smooth recovery for the combination of ketamine and diazepam due to the synergistic effect of both . In (Ket +Fen) group, the recovery was restless and berserk and that like the result was observed by [12, 13, 14].

In (Ket) group, Using ketamine as a sole anesthetic agent is usually associated with a lot of problems such as weak muscle relaxation. This result is consistent with the study of [11].The (Ket + Dia) group produced good muscle relaxation that agrees with [15,33,34] who found good muscle relaxation for the combination of ketamine and diazepam due to the synergistic effect of both . In (Ket+Fen) group the muscle good relaxation .

The reflexes of the eyes (Eyelids and Corneal) never disappeared in all the treatment groups , these result has an agreement with [16] who found that typically , (Ket) produced a state of catalepsy in which the eyes remain open, whereas the corneal and light reflexes remain intact. In (Ket+Dia) group, The eye remains fixed and central during anesthesia and the disappear of the corneal and palpebral reflexes is variable these result has an agreement with [17] , it is important to protect from accidental injury by either application of ophthalmic ointment or taping the eyelids closed with micropore tape.

In (Ket) group, the pupils size increases (mydriasis) due to the effect of ketamine on Muscarinic acetylcholine receptor and these result is show in all other groups at 5minutes after I.M administration anesthetic drugs, these results are consistent with [18]. (Ket+Fen) groups the pupils size decreases at 10-40 minutes after I.M injection causing constriction (miosis) of the pupils that agrees with [19] because Opioids μ -receptors induce pupillary constriction (miosis) that results from net excitation of parasympathetic nerves that innervate the pupil, leading to contraction of the pupillae sphincter (constrictor) muscle and block the activity of inhibitory interneurons (GABA), resulting in the increase of parasympathetic outflow and miosis.

The (Ket) group shows light analgesia, these result agrees with[20], who found that ketamine produces profound analgesia but with tonic-clonic spasm and without muscle relaxation of limb muscle, the analgesic effects of ketamine are thought to be mediated by binding of the drug to (NMDA) receptors and inter action with mu(μ) delta (δ) and kappa (κ) receptor .In (Ket+Dia) group the analgesic effect started at 5-20 and decreased gradually, these result agrees with [21], Diazepam and midazolam are effective sedatives in rabbits. They produce good muscle relaxation and potentiate the effect of anesthetics and narcotic analgesics .In (Ket+Fen) group the analgesia starts at 10 minutes after IM injection and

continues between 20-30 minute then decreases gradually, these results agrees with [22]who found that fentanyl greatly potentiate the analgesic activity of ketamine in rabbit.

There are interactions between opiate receptors and spinal cord .There was mildly a decrease of body temperature with (ket) alone these, results are consistent with [23] who found a thermoregulatory depressant effect of ketamine,while (Ket + Dia) rectal temperature decreased gradually at 5 minute to 60 minute. The decrease in rectal temperature was probably occurred as a result of administration of benzodiazepines derivatives (diazepam) because of central nervous system depression and a reduction of muscular activity these result agree with [11] . In (Ket+Fen) group, body temperature does not decrease severely but gradually at 20 minutes to 60 minutes these results agrees with[24] .That opioids appear to alter the equilibrium point of the hypothalamic heat-regulatory mechanism resulting in reducing body temperature.

All rabbits were showing tachypnea before induction anesthetic drugs , in (ket) group, the respiratory rate decreases between 5- 30 minutes and returns to the normal level gradually at 40-60 minutes these results agrees with [25]who found that Low doses of ketamine to the rabbit results in a decreased respiratory rate and Po₂ due to the effect of ketamine on NMDA- receptor .In (Ket+Dia) group, the respiratory rate decreases at 5-40 minutes that results are consistent with[26]who found that the diazepam and ketamine combination causesrespiratory depression . The respiratory rate decrease mildly in level at 5-20 minutes. In (Ket+Fen) , respiratory rate drop sharply at (5-30) minutes and increases gradually to the normal range ,this result agrees with [27]who found that the fentanyl can induce respiratory depression and it causes profound depression of the central nervous system, including the respiratory centres in the brain stem, and respiratory depression because of the effect of fentanyl on μ - receptors and ketamine on NMDA- receptor .

In (Ket) group the increase of heart rate at 5-20 minutes and decreases at 30 minutes while at 40-60 the heart rate is stable. Ketamine can increase the heart rate consequently increasing cardiac output and blood pressure that agrees with [28],while in (Ket+Dia) group after I.M injection the heart rate changed at 10-20minutes and at 30-60minutes with stable range these results agrees with[11,26]that the benzodiazepainedervitave causes minimal cardiovascular depression and Ketamine able to temporary counteract the bradycardia produced by diazepam, where ketamine stimulates the central sympathetic outflow, which in turn, causes stimulation of the heart .In (Ket+Fen) group, the heart rate mild increases these results agrees with [14] .

The effects of commonly used anesthetics on biochemical parameters of rabbits are poorly understood, plasma ALT and AST concentrations were within normal range for this species. In (ket) group, there is mildly change in the level of AST and ALT that agrees with [29]. The single administration of ketamine in rats shows no significant changes in AST and ALT, while (Ket+Dia) group shows decrease in the level plasma of AST and ALT these results disagreement with [14,30] who noticed the increase in plasma level of AST and ALT when used ketamine and diazepam due to hypotension and observed hypoxemia after treatment by ketamine and toxic effect of diazepam on liver cells. In (Ket+Fen) group, the plasma level of AST and ALT mildly increase. but all these changes were within biologically acceptable limits, this is may be due to reaction to the blood collection, causing some local muscle trauma, might also be responsible for the changes of these values. It is evident that the single dose of combination anesthetic drugs had no significant effect on rabbits liver.

CONCLUSIONS

The (Ket), (Ket+Dia), and (Ket+Fen) groups was good in protocol for Induction of anesthesia while the (Ket+Dia) group was a best combination for general anesthesia, is agreeable anesthesia time for short operation with good muscle relaxation and long recovery time when compared with other groups of experimental, the (Ket+Fen) group has showed suitable analgesia but long recovery time, (Ket+Dia) group showed significant decrease in the body temperature, the (Ket+Fen) showed significant decrease in respiratory rate. All groups showed increase and then decrease in heart rate that mean no significant change due to the heart rate with normal range, no significant differences in the serum level of ALT and AST between all treatment groups.

استخدام الكيتامين كعامل مخدر في الأرنب (دراسة مقارنة لمزيج الكيتامين مع الفنتانيل والكيتامين مع الدايازيبام) ودراسة بعض المعايير الفسلجية والكيموحيوية

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الخلاصة

أجريت الدراسة في البيت الحيواني لكلية الطب البيطري وتهدف الى معرفة تأثير دواء الكيتامين كعامل مخدر في الأرانب و المقارنة بين عدة أنواع من أنظمة التخدير العام في الأرانب ودراسته بعد مزجه مع دواء الدايازيبام والفنتانيل ، لقد استخدم لهذه الدراسة (32) أرنباً بالغاً محلية من كلا الجنسين وكانت معدل اوزانها تتراوح بين (1000-1900) غرام، تم حقنها بطريقة الحقن العضلي، وتم توزيعها عشوائياً وبأعداد متساوية في اربع مجاميع (8) أرانب في كل مجموعة. تمت دراسة فترة أحداث التخدير وطول فترة التخدير و وقت الافاقة وكذلك تمت دراسة بعض المعايير الفسلجية مثل معدل ضربات القلب ومعدل التنفس ودرجة حرارة الجسم، وكذلك تم تسجيل درجة التسكين ودرجة ارتخاء العين ومنعكسات العين (الجفن والقرنية والبؤبؤ). تم تسجيل هذه المعايير قبل الحقن بالعضلة (وقت الصفر) وبعد الحقن بالعضلة حسب الأوقات التالية (5، 10، 20، 30، 40، 50، 60) دقيقة حتى استجابة الأرانب للمؤثرات الخارجية. الفحوصات الكيمو حيوية (إنزيم ناقلة أمينوالإسبارتات، إنزيم ناقلة أمينوالألانين).

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