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Treatment of carnitine deficiency

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Summary: Carnitine deficiency is a secondary complication of many inborn errors of metabolism. Pharmacological treatment with carnitine not only corrects the deficiency, it facilitates removal of accumulating toxic acyl intermediates and the generation of mitochondrial free coenzyme A (CoA). The United States Food and Drug Administration (US FDA) approved the use of carnitine for the treatment of inborn errors of metabolism in 1992. This approval was based on retrospective chart analysis of 90 patients, with 18 in the untreated cohort and 72 in the treated cohort. Efficacy was evaluated on the basis of clinical and biochemical findings. Compelling data included increased excretion of disease-specific acylcarnitine derivatives in a dose–response relationship, decreased levels of metabolites in the blood, and improved clinical status with decreased hospitalization frequency, improved growth and significantly lower mortality rates as compared to historical controls. Complications of carnitine treatment were few, with gastrointestinal disturbances and odour being the most frequent. No laboratory or clinical safety issues were identified. Intravenous carnitine preparations were also approved for treatment of secondary carnitine deficiency. Since only 25% of enteral carnitine is absorbed and gastrointestinal tolerance of high doses is poor, parenteral carnitine treatment is an appealing alternative therapeutic approach. In 7 patients treated long term with high-dose weekly to daily venous boluses of parenteral carnitine through a subcutaneous venous port, benefits included decreased frequency of decompensations, improved growth, improved muscle strength and decreased reliance on medical foods with liberalization of protein intake. Port infections were the most troubling complication. Theoretical concerns continue to be voiced that carnitine might result in fatal arrhythmias in patients with long-chain fat metabolism defects. No published clinical studies substantiate these concerns. Carnitine treatment of inborn errors of metabolism is a safe and integral part of the treatment regime for these disorders.

Carnitine is a natural substance required for the bidirectional transport of acyl groups across the inner mitochondrial membrane. Acyl groups are transferred from coenzyme A (CoA), which cannot cross the inner mitochondrial membrane. Carnitine acyltransferases I and II and translocase are required for this transport.

Carnitine allows for the delivery of long-chain fatty acids for β-oxidation and the removal of acyl-CoA derivatives. This process allows for removal of metabolites that accumulate with fatty acid oxidation defects and organic acidurias. Availability of free carnitine is necessary for the maintenance of the normal acyl-CoA/free CoA ratio within the mitochondria.

Carnitine is available from the diet, with the major sources being red meats and dairy products, and is synthesized endogenously from methylated lysine residues released during protein degradation. The initial steps of synthesis are in muscle with the final step in liver, brain and kidney. Carnitine is filtered readily by the glomerulus and 95% of free carnitine is reabsorbed in the proximal tubule, with the majority of acylcarnitine derivatives being excreted (Rebouche and Paulson 1986).

Primary carnitine deficiency (McKusick 212140) due to an inborn error of carnitine synthesis has not been reported in man. Active transport of carnitine across the cell membrane occurs via a membrane transporter and genetic deficiencies of transporter activity represent the only known forms of primary carnitine deficiency (Pons and De Vivo 1995).

The selective excretion of acylcarnitine provides a route for removal of accumulating intermediates in metabolic disorders (Siliprandi 1986) Analysis of these acylcarnitine species in the blood and urine provides a diagnostic approach to these metabolic disorders (Rinaldo et al 1999). Excessive loss of these specific acylcarnitines in the urine results in loss of free carnitine and increases the probability of secondary carnitine deficiency (Pons and De Vivo 1995).

Secondary carnitine deficiency can result from poor diet or malabsorption of carnitine, or from increased renal tubular loss of free carnitine (Fanconi syndrome), haemodialysis, peritoneal dialysis, or the increased excretion of acylcarnitines with certain drugs. The US FDA has approved the use of carnitine for the treatment of renal dialysis-induced secondary deficiency. Controversy continues over treatment of patients with nonmetabolic causes. Caution should be taken to avoid extrapolating negative or positive data on carnitine treatment outcomes in such patients compared to those with an inborn error of metabolism (Bohan et al 2001; Bonner et al 1995; Pons De Vivo 1995; Shapira and Gutman 1991; Winter et al 1987).

Carnitine deficiency is diagnosed by anaylsis of total, free and acylcarnitine levels in tissues, including plasma. Since 95% of total body carnitine is in muscle, muscle carnitine analysis is the definitive diagnostic test. Plasma may be substituted and plasma carnitine deficiency is defined as a free carnitine value of 20 μmol/L or lower or an acyl/free carnitine value of 0.4 or higher (insufficiency) (Winter et al 1987). Decreased plasma carnitine correlates positively with muscle carnitine levels, but it must be emphasized that normal plasma carnitine does not rule out muscle deficiency. Therefore, if carnitine deficiency is suspected and plasma levels are normal, muscle biopsy is necessary to confirm the deficiency (Shapira and Gutman 1991).

CLINICAL EXPERIENCE

Carnitine deficiency was first described in 1965; by 1987, 36 cases had been reported in the literature. All cases had carnitine deficiency identified in muscle tissue and in

89% the plasma carnitine was also deficient. In many, only total carnitine was measured, which would miss a free carnitine deficiency associated with increased acylcarnitine. The symptoms of the 36 patients included encephalopathy in 77%, progressive muscle weakness in 77%, excess of lipid in muscle in 100% and cardiomyopathy in 23%. In 51 cases with plasma free carnitine deficiency, the clinical presentation was similar to that of the first 36 patients, with hypotonia and gross motor delay in 85%, failure to thrive in 75%, recurrent infections and metabolic decompensations in 85%, mental retardation in 40%, encephalopathy in 5%, and cardiomyopathy in 30% (Winter et al 1987).

Our first patient identified with carnitine deficiency was affected with methylmalonic aciduria (MMA), mutase 0 methylmalonic aciduria (MMA)(McKusick 251000). This boy was born in 1982 and initial treatment consisted of dietary precursor restriction and cyanocobalamin. Initial response to dietary therapy was promising and, by 5 months, growth, development and overall health were good. However, the long-term prognosis for this metabolic disorder was generally felt to be poor, with nearly all cases fatal in infancy or early childhood. Between the ages of 5 and 9 months, he experienced severe loss of weight, muscle mass and strength, with recurrent episodes of metabolic decompensation and persistent neutropenia. Recent reports of carnitine deficiency in his disorder and other organic acidopathies prompted analysis of his plasma carnitine levels. Carnitine deficiency was confirmed, with plasma free carnitine value of 7.9 μmol/L and acylcarnitine of 9.5 μmol/L. Treatment with oral carnitine was begun at age 9 months and the dose was gradually increased from 25 to 200 mg/kg per day. The dose was increased until normal plasma free carnitine levels were achieved. With normalization of plasma free carnitine levels by 12 months of age, the patient resumed normal growth and development, neutropenia resolved, and the frequency of decompensation episodes decreased significantly.

SECONDARY CARNITINE DEFICIENCY SAFETY AND EFFICACY STUDIES

Treatment of secondary carnitine deficiency due to inborn errors of metabolism with oral carnitine was approved by the FDA in 1992. The new drug application was limited to metabolic disorders in which acyl-CoA metabolites accumulate. This orphan drug approval was based on evidence from retrospective chart analyses of 90 patients. Two carnitine-treated patient cohorts with either biochemical (26) or clinical (48) evidence of efficacy were compared to a historical cohort of untreated control patients.

The historical cohort consisted of 18 patients: propionic acidaemia (10) (McKusick 606054), methylmalonic acidaemia (5) and glutaric aciduria type II (3) (McKusick 602473). Fifteen patients were from the University of California, San Diego (UCSD) and 3 from the Children's Hospital Central California (CHCC). Treatment included medical foods, specialized formulas, vitamin cofactors, alkali supplementation and anticonvulsants. Recurrent episodes of metabolic decompensation were reported in 8, and 10 had seizures. Eight patients had been mentally retarded and 9 had failure

to thrive. All 18 patients died of their disorder; 12 prior to age 2 years and 6 between ages 2 and 17 years.

Of the 48 patients in the clinical efficacy treatment cohort, 19 were from CHCC, 11 from UCSD, 3 from Oregon Health & Science University (OHSU) and 15 from Duke University. Metabolic disorders included glutaric aciduria type II (12) (including ethylmalonic aciduria), methylmalonic acidaemia (11), medium-chain fatty acyl-CoA dehydrogenase deficiency (8) (MCAD) (McKusick 201450), propionic acidaemia (6), isovaleric acidaemia (3) (McKusick 2435000), β-ketothiolase deficiency (3) (McKusick 203750), glutaric aciduria type I (2) (McKusick 231670), short-chain fatty acyl-CoA dehydrogenase deficiency (1) (SCAD) (McKusick 606885), hydroxymethylglutaryl-CoA lyase deficiency (1) (McKusick 246450) and 3-hydroxyisobutyric aciduria (1) (McKusick 236795).

In 20/48 patients the free carnitine value was below 20 μmol/L (mean $\pm$ 2SD = 25.4 ± 17.3 μmol/L). Twenty-five of the 48 had an acyl/free carnitine ratio greater than 0.4 (mean $\pm$ 2SD = 1.11 ± 1.82). Hospitalization frequency data pre- and post-initiation of carnitine treatment were available on 15 patients, with a reduction from 0.491 to 0.075 admissions per month. In 8 out of 14 patients with failure to thrive, the weight increased to above the 5th centile for age with carnitine treatment. As compared to death in all 18 patients of the historical cohort, only 2 of the 48 patients had died from their disorder within the minimum follow-up of 2 years.

Twenty-six patients were included in the cohort for biochemical evidence of efficacy. Twelve patients were from Duke University, 11 from CHCC, and 3 from UCSD. The diagnoses were propionic acidaemia (5), methylmalonic acidaemia (7), glutaric aciduria type II (5), MCAD (5), β-ketothiolase deficiency (2), isovaleric acidaemia (1) and hydroxymethylglutaryl-CoA lyase deficiency (1). Fifteen of the 26 patients had plasma free carnitine values below 20 μmol/L and 20/26 had an elevated acyl/free plasma carnitine ratio greater than 0.4. Hospitalization frequency dropped from 0.319 to 0.047 days per month after starting carnitine treatment. Resolution of failure to thrive with weight crossing from below to above the 5th centile was seen in 5/9 patients.

Increased excretion of disease-specific acylcarnitine species occurred in 12 patients. Lowering of levels of accumulating intermediate metabolites was documented in 11/26 patients. One patient with MCAD demonstrated decreased ability to generate ketone bodies on fasting, with restoration of ketosis after an oral carnitine load of 100 mg/kg. In a patient with glutaric aciduria type II presenting with cardiomyopathy, carnitine therapy was associated with an increased urinary excretion of glutarylcarnitine and normalization of the cardiac ejection fraction. The patient with isovaleric acidaemia had increased excretion of isovalerylcarnitine. In three patients, hippuric acid excretion increased, demonstrating increased availability of mitochondrial free CoA facilitating synthesis of hippuric acid from benzoyl-CoA and ammonia.

Adverse events for this 26-patient cohort included vomiting in 37%, diarrhoea in 23%, abdominal pain in 12%, fishy odour due to trimethylaminuria (McKusick 602079) in 12% and one patient (4%) with transient alopecia and rash. One patient with propionic acidaemia died.

Trimethylaminuria was reported in 7% of all patients in both treatment cohorts. In the bowel, carnitine is converted by bacteria to trimethylamine. Since mutations of the flavin monooxygenase 3 gene (McKusick 136132) are frequent and associated with poor metabolism of trimethylamine, such patients are especially susceptible to this odour problem. Treatment of patients with metronidazole aimed at reducing the bacterial load, and thus the trimethylamine load, rapidly resolves the odour problem in most patients. Oral metronidazole doses of 125–250 mg once daily for a course of 10 days, with repeated courses when odour recurs, allow for continued oral carnitine therapy.

ROUTINE LONG-TERM INTRAVENOUS CARNITINE THERAPY

In one patient from the NDA biochemical cohort with MMA(mut0), carnitine was administered in varying oral and intravenous doses and urinary excretion of propionylcarnitine was quantified daily. As can be seen in Table 1, a clear dose–response effect can be identified, with increasing excretion of propionylcarnitine proportional to the increasing dose and availability of carnitine. As would be expected from the known poor absorption of oral carnitine (25% of intake absorbed), 300 mg/kg per day of oral carnitine resulted in a similar excretion of propionylcarnitine as did 100 mg/kg per day of intravenous carnitine. Also of interest is the initial high excretion of propionylcarnitine associated with intravenous carnitine therapy and the eventual stabilization of this excretion after 2 weeks of treatment. This suggests the patient had an excess of propionyl-CoA derivatives to excrete initially and that high-dose intravenous carnitine was required to reach equilibrium. Clinically, the patient showed rapid reversal of muscle weakness, failure to thrive and cardiomyopathy. This patient has continued on weekly intravenous

Table 1 Urinary concentration of propionyl carnitine and MMA in 24 hours relative to route and dose of carnitine administered

	Carnitine dose (mg/kg per day)		*Propionylcarnitine*	*Methylmalonic acid*
Day	*Oral*	*IV*	(μmol/mg *creatinine*)	(μmol/mg *creatinine*)
1	400		15.9	199.0
2	0	0	5.0	86.4
3		100	8.9	34.6
4		200	38.9	94.8
5		300	43.7	97.8
6		300	63.4	97.3
7		300	68.5	127.3
8		300	45.4	89.3
9	400	300		
14	666	300		
18	666		14.3	

carnitine treatment of 300 mg/kg for the past 10 years. This has been associated with the ability to tolerate a normal protein intake without special formulas or medical foods. Renal function has also remained normal.

Some patients do not tolerate enteral carnitine therapy well or cannot achieve adequate detoxification with oral carnitine. This is especially true in patients with inborn errors of metabolism for which high doses of oral carnitine are required, such as MMA and propionic aciduria. In such patients, intravenous carnitine at doses up to 300 mg/kg per day are useful for both acute resuscitation and long-term therapy. Long-term intravenous carnitine therapy via a surgically inserted venous access port is an alternative long-term therapeutic option. Owing to the risk of infection associated with indwelling venous access ports, we reserve this form of therapy for our severely ill metabolic patients.

Prior surgical insertion of the port, our patients must successfully complete and tolerate a one-month course of parenteral carnitine by peripheral intravenous route. Carnitine is infused at a dose of 300 mg/kg over 20 minutes to a few hours and is usually diluted in a 5% dextrose solution. Carnitine infusion frequency varies from once weekly to daily, depending on the clinical needs. Owing to an initial observation of an increased incidence of port infections when access needles were left in the port between infusions, we require insertion and removal of each needle with each infusion. Monthly blood cultures are obtained from the port site and infections are treated aggressively. The use of monthly thrombolytic treatments, such as urokinase, has lessened the frequency of port infections.

We have reviewed the data on seven long-term (2–10 years) parenterally treated patients at CHCC: propionic acidaemia (2), methylmalonic acidaemia (3), 3-methylglutaconic aciduria (1) (McKusick 250950) and cytochrome oxidase deficiency (1) (McKusick 220110). Clinical response to chronic parenteral therapy included decreased hospitalization frequency (7), improved muscle strength (5), improved weight gain (4), improved dietary protein tolerance (4), and improved renal function (1, MMA). Three patients in this group died. After 8 years of daily intravenous carnitine treatment, a patient with propionic acidaemia died with cardiomyopathy. Benefits of her intravenous treatment included radiological resolution of osteoporosis, reduction of decompensation frequency from over 100 events yearly to fewer than 10, increased natural protein intake by mouth and improved stamina allowing her to attend normal school. Another patient with propionic acidaemia died while on vacation of cardiomyopathy a year after discontinuing parenteral carnitine treatment. Treatment was discontinued at the parents' request following a port infection. After discontinuation of treatment, he required increasing protein restriction and experienced multiple hospitalizations. The patient with cytochrome oxidase deficiency died from respiratory failure after 10 years of treatment. Four patients are continuing treatment. One is the previously mentioned 20-year-old patient with MMA (mut0) who consumes a normal protein diet, attends college, has normal renal function and has had no episodes of decompensation for over 7 years. He currently receives a single weekly dose of parenteral carnitine of 300 mg/kg through the initial port inserted 10 years ago. In addition to the benefits derived from parenteral carnitine treatment, all patients have benefited from easy

venous access, allowing at-home fluid resuscitation and antibiotic treatment without hospitalization and disruption to normal family routine.

In recent years, the safety of carnitine treatment in patients with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) (McKusick 600890) has been questioned (Jackson et al 1991; Tyni et al 1997). This was again raised in the January 2002 edition of *Pediatrics* (den Boer et al 2002). The authors reported no statistically significant differences in the frequency of metabolic decompensations or muscle cramping between carnitine supplemented and unsupplemented groups but still advised against supplementation on the basis of previously reported theoretical concerns of cardiac arrhythmia and no clear benefit noted with supplementation.

These theoretical concerns with LCHAD have raised safety concerns regarding carnitine treatment of any patients with cardiomyopathy. In particular, such concerns have been extrapolated to most paediatric cardiomyopathy patients, in whom LCHAD is only rarely the cause and the addition of carnitine therapy may prove beneficial.

Carnitine was approved by the FDA as safe and efficacious for the treatment of fatty acid oxidation defects and organic acidurias. No significant safety concerns were identified in all patients treated, including 3 with LCHAD.

Concern regarding carnitine treatment of patients with LCHAD is based on data from animal models of cardiac ischaemia. During the period of reperfusion of the damaged cardiac tissue, fatty acid oxidation occurs at the expense of glucose oxidation. Accumulation of long-chain carnitine esters occurs and these are possibly arrhythmogenic (Corn and Yamada 1995).

These studies have been extrapolated to LCHAD patients, in whom carnitine supplementation might increase formation of long-chain carnitine esters and precipitate a life-threatening arrhythmia. To date, no studies of cardiac arrhythmia associated with carnitine therapy in LCHAD have been reported. The significance of a few anecdotal case reports of arrhythmia with carnitine treatment is clouded by published reports of fatal cardiac arrhythmias in LCHAD patients not receiving carnitine (Bonnet et al 1999; Jackson et al 1991; Rocchiccioli et al 1990; Tyni et al 1997).

Proponents of carnitine treatment for cardiomyopathy due to LCHAD cite the beneficial effects of carnitine in restoring mitochondrial energy metabolism through excretion of long-chain acylcarnitine derivatives. Since free carnitine is lost in this process, pharmacological and not physiological amounts of carnitine are needed to allow this detoxification to continue and to prevent deficiency (Colonna and Iliceto 2000; Helton et al 2000; Lango et al 2001). The low incidence of LCHAD precludes the use of a prospective double-blind placebo-controlled drug trial. It is therefore necessary to rely on medical evidence gathered from trials of related medical conditions, patient reports, and retrospective reviews.

In a large prospective trial of carnitine for the treatment of myocardial infarction in adults in Italy, the CEDIM trial, patients were given carnitine or placebo at the time of the acute infarction event. Carnitine was shown to improve both end-diastolic and systolic volume in the carnitine-treated patients versus placebo, reflecting improved cardiac function. The incidence of arrhythmia was not increased

in the carnitine-treated cohort (Colonna and Iliceto 2000). Investigators have reported protective effects of carnitine in ischaemic heart disease, with improved glucose metabolism, reduction of toxicity from long-chain acyl-CoA and acyl-carnitine derivatives, improved coronary blood flow and an antiarrhythmic effect. In the retrospective case reports submitted for approval of oral and intravenous forms of carnitine in the United States, no cardiac arrhythmias were documented in any treated patients and no deaths were felt to be attributable to carnitine administration (Helton et al 2000; Lango et al 2001).

In the paper by den Boer and colleagues (2002), information on 50 patients with LCHAD from Europe, the United States, Australia and Israel was gathered by questionnaire. Nineteen patients were deceased (38%); 14 died prior to the diagnosis; of the remaining 5, 3 died from cardiomyopathy, 1 from sudden death, and 1 with hepatic failure. Of the 31 surviving patients, 12 were treated with oral carnitine (50–100 mg/kg per day). No statistically significant difference in morbidity and/or muscle cramping was detected between those receiving and those not receiving carnitine supplements. The authors conclude that there is no evidence to support the use of carnitine treatment in LCHAD; however, they reported no increase in morbidity or mortality in the carnitine-treated patients (den Boer et al 2002).

In March 2002, I requested information regarding negative experiences, including arrhythmias, associated with carnitine therapy of LCHAD from the subscribing members on Metabol-I, a popular Internet list server for metabolic specialists. There were no adverse events reported by these members.

In March 2001, on the fatty acid oxidation parents group web site, information—both positive and negative—was requested regarding response to carnitine supplementation in patients with fatty acid oxidation defects including LCHAD. Data were obtained on 15 patients: 5 with LCHAD, 9 with MCAD and 1 with trifunctional protein (TFP) deficiency (McKusick 600890). All LCHAD patients had been supplemented with carnitine during the course of treatment and 3 were being treated at the time of the survey. One was 13-year-old male who had been on carnitine for 7 years with no complications. Another was a 10-year-old male who had taken carnitine for 8.5 years; he had been taken off carnitine for 12 months because of muscle cramping and no cramping or complications recurred upon restarting. The third was an 8-year-old male on carnitine treatment for 7.5 years; he had muscle cramping initially and some gastrointestinal upset but no complications since.

Two LCHAD patients reported negative effects. A 5-year-old female had taken carnitine for two brief periods at 14 and 17 months of age and experienced a rapid decrease in muscle strength on carnitine therapy that improved once off carnitine. The second patient, an 8-year-old female, was supplemented from 17 months to 5 years of age. Muscle cramping led to the discontinuation of therapy and the cramping improved once off supplementation.

Nine MCAD cases, all supplemented for more than a year, were identified. The only complications were muscle cramping and pain in one patient, body odour in 4 and gastrointestinal upset in 3. All patients reported a benefit from supplementation: increased stamina (4), increased muscle strength (3), increased

alertness (3), decreased irritability (2) and decreased episodes of hypoglycaemia (2). The one TFP patient, a 22-year-old female, reported 15 years of carnitine supplementation without complications.

In a 10-year retrospective chart review of 221 paediatric patients with cardiomyopathy from seven US medical centres, 76 of the patients had received carnitine therapy, including 3 with LCHAD, and 145 patients had not received carnitine therapy, including 3 LCHAD patients. The results of this study showed no deaths or arrhythmias attributable to carnitine therapy. There was a statistically significant improvement in cardiac function and clinical status in the patients receiving carnitine. During the first 100 days of treatment, those receiving carnitine therapy had a statistically improved survival rate, with the long-term survival rate of both groups being equal (Helton et al 2000).

CONCLUSION

Carnitine deficiency is a frequent secondary complication in patients with metabolic errors of fatty acid oxidation or organic acid metabolism. The selective excretion of the acylcarnitines in the urine provides a detoxification mechanism, but at the expense of loss of free carnitine. Treatment with pharmacological doses of carnitine not only prevents carnitine deficiency, it allows for excretion of toxic acyl groups.

Although theoretical concerns about cardiac arrhythmias have been raised concerning carnitine supplementation of LCHAD patients, no clinical studies or reports can be cited that clearly either substantiate or refute these concerns. Carnitine treatment of paediatric cardiomyopathy has been shown to lower the mortality rate during the first 100 days of therapy and to improve cardiac and clinical function (Helton et al 2000). Certainly, a cautious concern and surveillance of patients receiving carnitine therapy for LCHAD is warranted. However, denial of potentially life-saving carnitine supplementation on theoretical grounds to all patients with cardiomyopathy does not appear to be substantiated at this time.

The US Food and Drug Administration approved carnitine as a safe and efficacious treatment for secondary carnitine deficiency due to fatty acid oxidation defects and organic acidurias. Because of the lack of adequate numbers of patients in controlled settings with metabolic diseases, the high genetic and clinical variability within each enzymatic disorder, the potentially fatal nature of these disorders, the fact that carnitine is a natural substance with normal tissue values and the known lethality of carnitine deficiency, double-blind placebo-controlled studies were judged unethical and unsafe by the metabolic consultants and the FDA panel involved in the secondary deficiency NDA submission. Metabolic specialists continue to cite this lack of controlled studies as a reason to question the efficacy of carnitine treatment of metabolic disorders. This is particularly interesting in view of the fact that few, if any, of our treatment regimes have undergone the scrutiny of a double-blind placebo-controlled trial for safety and efficacy. Certainly, as with all our therapies—both dietary and pharmaceutical—we must strive for more objective data, while continuing to rely on existing data supporting

the safety and efficacy of carnitine treatment of these potentially fatal metabolic disorders.

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