Effects of L-Carnitine on Arrhythmias during Hemodialysis

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SUMMARY

The therapeutic effect of L-carnitine on arrhythmias during hemodialysis was evaluated in 17 patients with chronic renal disease undergoing intermittent hemodialysis. In 11 of 17 patients (65%), ventricular or supraventricular premature beats appeared at 20 to 30 min after the start of hemodialysis and continued throughout the dialysis. Plasma carnitine was at a lower level in the predialysis period (24.8 ± 7.9 n mole/ml) as compared with the normal human levels (46.1 ± 8.6 n mole/ml), and decreased markedly by the end of dialysis (8.2 ± 5.9 n mole/ml). Plasma free fatty acids rapidly increased immediately after the start of dialysis, reached the maximum levels after 20 min (from 0.23 ± 0.09 to 1.31 ± 0.64 mEq/L) and maintained higher levels even at the end of dialysis (0.76 ± 0.29 mEq/L). Administration of L-carnitine (2 Gm orally), 2 hours before the start of dialysis, maintained plasma carnitine within normal levels throughout the dialysis and suppressed the increase in plasma free fatty acids. Both the incidence and the severity of premature beats during hemodialysis were significantly reduced by oral administration of L-carnitine (2 Gm daily) for 4 to 8 weeks. These results suggest that L-carnitine is useful for the treatment of hemodialysis arrhythmias, presumably by restoring impaired oxidation of free fatty acids.

Additional Indexing Words:

Holter electrocardiography High plasma free fatty acids

A marked depletion in blood carnitine has been reported in the patients undergoing hemodialysis,[1)-4)] and it was suggested as one of the causes of some complications of hemodialytic treatment.[2)] Because carnitine is

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essential for the oxidation of free fatty acids (FFA) in mitochondria, oxidation of FFA may be impaired in patients treated with hemodialysis.

Although high concentration of FFA have also been reported to provoke some arrhythmias in ischemic heart disease,[5)-9)] it was proposed that any deleterious effects of high FFA on the ischemic myocardium was due not to the FFA themselves but to the accumulation of intermediates subsequent to impaired FFA oxidation.[10)] Because most patients undergoing hemodialysis have cardiovascular complications,[11)] the reduced carnitine and heparin-induced high plasma FFA are supposed to provoke some arrhythmias during hemodialysis in those patients. The purpose of this study was to observe the relationship between hemodialysis arrhythmias and plasma levels of carnitine and FFA, and to evaluate the therapeutic effect of L-carnitine on the arrhythmias.

Patients and Methods

Seventeen patients with chronic renal disease (9 men, 8 women) and undergoing hemodialysis 3 times a week were studied (Table I). All patients

Table I. Clinical Features of Subjects

Case	Age	Sex	Time on Hemodialysis (years)	Dialyser	Diagnosis on Routine ECG	Arrhythmia during Hemodialysis
1.	63	M	5.0	Plate GL	SVPB	SVPB
2.	59	F	3.5	Plate 1.0	SVPB	SVPB
3.	54	M	1.4	AM-10	old MI	VPB
4.	40	F	2.7	Plate 1.0	ST dep, VPB	VPB
5.	63	F	0.9	AM-10	ST dep	VPB
6.	35	F	3.7	AM-10	VPB	VPB
7.	49	M	5.7	Plate GL	ST dep, SVPB	VPB
8.	58	F	4.8	Plate GL	VPB	VPB
9.	62	M	4.6	AM-10	SVPB	VPB
10.	64	M	4.6	AM-10	old MI, VPB	VPB
11.	48	M	1.3	AM-10	VPB	VPB
12.	57	F	1.8	AM-10	VPB	
13.	28	M	4.8	Travenol	ST dep	
14.	29	M	0.3	Plate GL	ST dep	
15.	50	M	3.7	Plate GL	ST dep	
16.	48	F	0.6	Plate GL	ST dep	
17.	72	F	1.4	AM-10	TS dep	

Abbreviations: ECG=electrocardiogram; MI=myocardial infarction; ST dep=ST depression; SVPB=supraventricular premature beat; VPB=ventricular premature beat; Plate GL and Plate 1.0=multilayer plate kidneys; AM-10 and Travenol=hollow fiber artificial kidney.

had sporadic ventricular or supraventricular premature beats, or ST-T abnormalities in at least one of their previous electrocardiograms. The mean age was 52 years (range 28–72 years). The mean period for hemodialysis was 3.0 years (range 0.3–5.7 years). Multilayer plate kidneys or hollow fiber artificial kidneys were used for hemodialysis. Heparin (3,000 to 8,000 I.U.) was given intravenously as a bolus and was followed by a continuous infusion of 800 to 1,500 I.U. per hour throughout the hemodialysis. Patients were dialysed for 5 hours. Drug therapy was held constant throughout the study.

In all patients, the effects of L-carnitine on the plasma levels of carnitine, FFA, triglycerides, and electrolytes were studied in a single dose (2 Gm) and at a dose of 2 Gm daily for 1 week. Two Gm of L-carnitine (provided by Otsuka Pharmaceutical Factory, Naruto, Japan) was administered orally 2 hours before each dialysis session. Plasma levels of these metabolites were determined before and 10, 20, 30, 60, 180, and 300 min after the start of hemodialysis. Plasma carnitine was determined enzymatically by the method of Marquis and Fritz.[12] Serum FFA was determined by the method of Itaya and Ui[13] and triglyceride was determined enzymatically with a commercial kit (Eiken Chemical, Tokyo). Electrolytes were determined by the photometric method.

During hemodialysis, electrocardiograms were recorded continuously with DYNA-GRAM Holter recorder (Model 7100) and analysed by a DYNA-GRAM scanner (Model 6000, Instrument for Cardiac Research Inc, New York). In 8 patients (Cases 1–8) in whom a number of premature beats appeared during hemodialysis, L-carnitine was administered at a dose of 2 Gm daily for 8 weeks and Holter electrocardiograms were recorded at 1, 4, and 8 weeks of the treatment. All data were expressed as the mean and standard deviation of the mean. Statistical analysis was performed by paired or non-paired Student's t tests.

Results

Changes in plasma levels of various metabolites during hemodialysis:

Plasma levels of carnitine, FFA, and triglycerides during hemodialysis are shown in Table II. Plasma levels of carnitine were even low in the predialysis period as compared with the normal human levels (24.8 ± 7.9 and 46.1 ± 8.6 n mole/ml respectively, $p < 0.001$), and they decreased markedly by the end of hemodialysis. Serum levels of FFA rapidly increased immediately after the start of dialysis, reached a maximum level 20 min later and maintained an elevated level at the end of dialysis, as compared with the levels in predialysis period. Serum levels of triglycerides decreased gradually

Table II. Changes in Plasma Levels of Carnitine, FFA, and Triglycerides during Hemodialysis

	Carnitine (n mole/ml)	FFA (mEq/L)	Triglycerides (mg/100 ml)
Before hemodialysis	24.8±7.9	0.23±0.09	209±72
Hemodialysis 10 min	21.8±7.8*	1.26±0.39*	192±68*
20 min	20.6±6.7*	1.31±0.64*	183±66*
30 min	18.6±7.2*	1.22±0.64*	168±60*
60 min	14.3±7.0*	0.98±0.53*	137±40*
180 min	10.0±6.3*	0.79±0.34*	122±34*
300 min	8.2±5.9*	0.76±0.29*	125±37*

Values were represented as mean±SD.

Asterisks represent the significance of changes, compared with the levels before hemodialysis ($p<0.001$ by Student's t test)

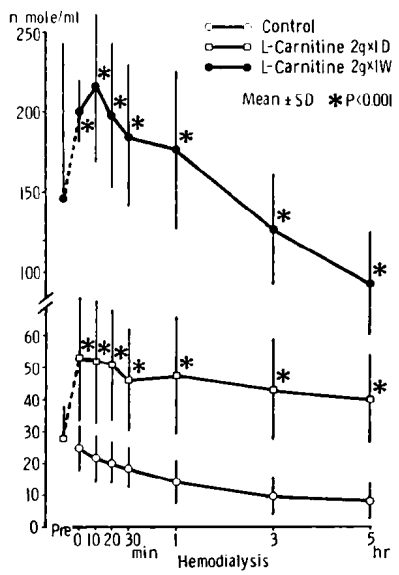

Fig. 1. Effects of L-carnitine on plasma carnitine levels. Abbreviations: Pre=before the administration of L-carnitine; 1D=a single dose; 1W=1 week. Asterisks represent the significance of changes (compared with the control) by Student's t test.

during hemodialysis, although they were higher than the normal levels during the predialysis period.

Effects of L-carnitine on the plasma levels of various metabolites:

A single dose (2 Gm) of L-carnitine increased plasma carnitine levels from 28.2±9.7 to 53.0±21.0 n mole/ml after 2 hours and maintained normal

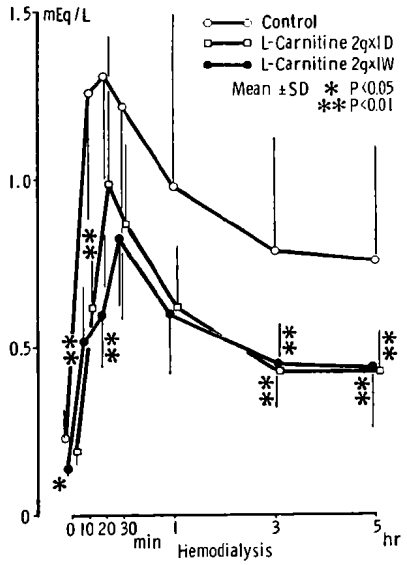

Fig. 2. Effect of L-carnitine on serum FFA levels. Abbreviations are identical to Fig. 1. Asterisks represent the significance of changes (compared with the control) by Student's t test.

levels throughout hemodialysis. After the administration of L-carnitine (2 Gm daily) for 1 week, plasma carnitine was maintained at much higher levels (Fig. 1).

As compared with the control value, the peak levels of FFA at 20 min after the start of hemodialysis tended to be decreased by L-carnitine. In addition, FFA levels at 3 to 5 hours after the start of dialysis were significantly lower in the groups treated with L-carnitine (Fig. 2). Serum levels of triglycerides and electrolytes were not affected by L-carnitine (Figs. 3, 4).

Arrhythmias during hemodialysis:

During hemodialysis, arrhythmias appeared in 11 of 17 patients (65%); 9 showed ventricular premature beats (VPBs) and 2 supraventricular premature beats (SVPBs) (Table I). In these cases, arrhythmias appeared within 20 to 30 min after the start of hemodialysis and continued throughout the dialysis. A representative case with ventricular premature beats is shown in Fig. 5.

Effects of L-carnitine on the hemodialysis arrhythmias:

Effects of L-carnitine on the hemodialysis arrhythmias were evaluated in 2 ways, between the groups and in individual cases. For the statistical analysis between the group treated with L-carnitine and an untreated control

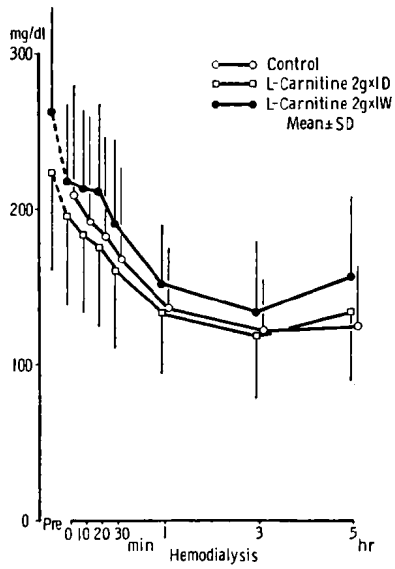

Fig. 3. Effects of L-carnitine on serum triglyceride levels. Abbreviations are identical to Fig. 1. No significant changes were observed, as compared with the control.

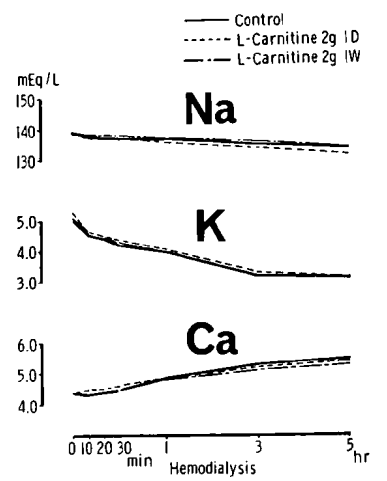

Fig. 4. Effects of L-carnitine on serum electrolytes levels. Abbreviations are identical to Fig. 1. No significant changes were observed, as compared with the control.

group, log (VPBs or SVPBs+1) was used in place of VPBs or SVPBs themselves. This transformation stabilized the variance and normalized the distribution. L-carnitine significantly decreased hemodialysis arrhythmias after 4 and 8 weeks of treatment (Fig. 6).

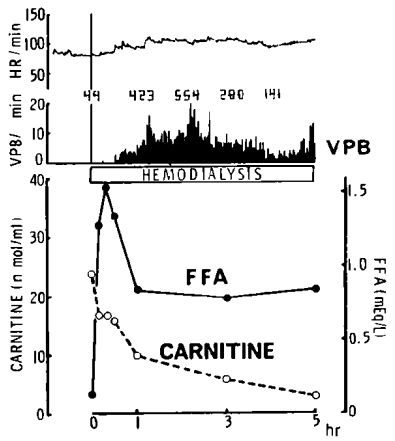

Fig. 5. A 40-year-old female with 2.7 year history of hemodialysis (Case 4). Ventricular premature beats during hemodialysis were shown on a histogram as the number per minute (a part of the trend chart automatically analysed by DYNA-GRAM Holter scanner Model 6000). Abbreviations: HR=heart rate; VPB=ventricular premature beat; FFA=free fatty acids.

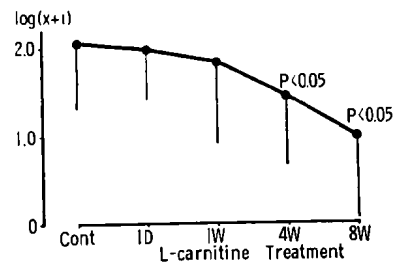

Fig. 6. Effects of L-carnitine on arrhythmias during hemodialysis. Values were represented as mean±SD. A student's paired t test was used for the significance of changes, compared with the control. Abbreviations: X= number of ventricular or supraventricular premature beats during hemodialysis; Cont=control.

In individual cases, a greater than 90% reduction in premature beats and a reduction in the severity of ventricular premature beats (grading system of Lown and Wolf)[14] were observed in 3 of 7 patients after 4 weeks and in 5 of 8 patients after 8 weeks (Tables III, IV).

Discussion

Since a reduction in plasma carnitine levels has been observed in patients undergoing hemodialysis and has been suggested as a cause of a number of

Table III. Effects of L-carnitine on the Percent Change of the Frequency of Hemodialysis Arrhythmias

Case	Hemodialysis Arrhythmia	Control	L-carnitine Administration			
			Single dose (%)	1 week (%)	4 weeks (%)	8 weeks (%)
1	SVPB	82	102 (+24)	129 (+57)	*	0 (−100)
2	SVPB	1073	201 (−81)	*	101 (−91)	0 (−100)
3	VPB	24	13 (−46)	0 (−100)	0 (−100)	0 (−100)
4	VPB	1507	613 (−59)	2277 (+51)	61 (−96)	74 (−95)
5	VPB	11	26 (+130)	31 (+182)	8 (−27)	0 (−100)
6	VPB	631	680 (+8)	607 (−4)	316 (−50)	343 (−46)
7	VPB	30	32 (+7)	34 (+13)	15 (−50)	43 (+43)
8	VPB	73	85 (+16)	63 (−14)	128 (+75)	86 (+18)
Mean			(±0)	(+26)	(−48)	(−60)

* No data available because of recorder malfunction.

Frequency of premature beats is represented by total number during hemodialysis. Percent change from control is expressed in parentheses.

Abbreviations are identical to Table I.

Table IV. Effect of L-carnitine on the Grade of Ventricular Premature Beats

Case	Hemodialysis Arrhythmia	Control	L-carnitine Administration			
			Single dose	1 week	4 weeks	8 weeks
1	SVPB	1	1	1	*	0
2	SVPB	2	2	*	1	0
3	VPB	1	1	0	0	0
4	VPB	4a	4b	4b	3	3
5	VPB	1	1	1	1	0
6	VPB	4a	4a	4a	2	4a
7	VPB	1	1	1	1	1
8	VPB	1	1	1	1	1

Grading of VPB by Lown and Wolf[14]:

Grade 0=no VPBs

Grade 1=isolated unifocal VPBs <30/hr or 1/min

Grade 2=isolated unifocal VPBs >30/hr or 1/min

Grade 3=multifocal VPBs

Grade 4a=couplets, Grade 4b=salvos

Grade 5=early VPBs (R on T)

SVPBs in this study were estimated by this grading system.

Abbreviations: SVPB=supraventricular premature beat; VPB=ventricular premature beat.

* No data available because of recorder malfunction.

undesirable symptoms,[2] it may be clinically beneficial to avoid the depletion of plasma carnitine.[15] For this purpose, restoration of plasma carnitine to normal levels has been tried by either oral or other mean of carnitine adminis-

tration.[15)-17)] However, there have been no reports on therapeutic effects in clinical trials, using the patients treated with hemodialysis. Since the D-form of carnitine has been reported to have no biological effects, and to competitively inhibit the uptake of L-carnitine in heart cells,[18)] L-carnitine was used in this study.

Reduction in the plasma levels of carnitine during hemodialysis is explained by the fact that carnitine is dialysed into the dialysate.[2)] Because a close correlation was observed between the peak levels of FFA and the levels of triglyceride during the predialysis period ($p<0.005$), the increase in plasma levels of FFA is explained by a conversion from triglycerides by heparin. Administration of L-carnitine significantly suppressed the increase in plasma FFA without affecting triglyceride levels. These findings indicate that the conversion from triglyceride to FFA remained unchanged, but the oxidation of FFA was accerelated by addition of L-carnitine.

Although much attention has been focused on the arrhythmogenic effect of excess FFA,[5)-9)] the FFA levels that induce arrhythmias in ischemic hearts do not always induce arrhythmias in normal hearts. The difference is supposed to depend on the tissue carnitine concentrations, namely lower concentrations in ischemic myocardium as compared with that in normal controls.[19)-25)] In ischemic and excess FFA supplemented dog hearts, pretreatment with L-carnitine prevented both the reduction in tissue carnitine concentrations and serious ventricular arrhythmias.[26)] These observations indicate that arrhythmogenesis of excess FFA may depend not only on the plasma FFA levels but also on the tissue carnitine that is regulating FFA oxidation. During peritoneal dialysis of rats, tissue carnitine concentrations in skeletal and cardiac muscle were reduced to two thirds of the levels in the predialysis period.[27)] In patients treated for a long time with intermittent hemodialysis, tissue carnitine concentrations in skeletal muscle were reduced to one tenth of that in controls.[2)] This low concentration in muscle cannot be explained by the loss of plasma carnitine during dialysis.[2)] As an explanation, it was suggested that the cellular mechanisms for concentrating carnitine had failed in those patients.[2)]

In most of our patients, arrhythmias appeared 20 to 30 min after the start of hemodialysis, a little later than the rapid increase in plasma FFA levels. This observation suggests that the occurrence of arrhythmias may be related to the accumulation of intermediates in FFA oxidation. Plasma carnitine levels were restored to normal human levels by oral administration of a single dose (2 Gm) of L-carnitine. Carnitine was maintained at much higher levels after 1 week of carnitine treatment, but antiarrhythmic effect were observed not in these periods but in later periods. The discrepancy

between the recovery of plasma carnitine levels and the delay in antiarrhythmic effects can be explained as follows. First, cellular uptake of carnitine is so slow that it takes time to restore tissue carnitine concentrations to normal levels. This explanation is supported by the suggestion of a failure of the cellular mechanisms for concentrating carnitine in the patients treated with long-term hemodialysis.[2] In 3 patients (Cases 6–8), L-carnitine did not prevent hemodialysis arrhythmias, in spite of the increase in plasma carnitine levels. In these patients, cellular mechanisms for concentrating carnitine may be extremely disturbed. Second, since arrhythmogenesis of excess FFA is probably due to the injury of cell membranes by the accumulated intermediates of FFA oxidation,[10] it takes time for carnitine to reduce the accumulated intermediates and allow for healing of the cell membranes.

Changes in electrolyte balance, pH or hemodynamics have been suggested as other causes of hemodialysis arrhythmias. In this study, however, plasma levels of electrolytes and pH were not changed by the administration of L-carnitine and hemodialysis procedures were not changed before and after carnitine treatment.

No undesirable side effects were obtained after 8 weeks of carnitine treatment. Administration of L-carnitine has been continued for 16 months without any side effects in 3 patients, because of improvement not only of hemodialysis arrhythmias but also of postdialysis syndrome. From these observations, it was concluded that L-carnitine is useful for the treatment of hemodialysis arrhythmias, presumably by restoring impaired FFA oxidation.

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