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Pharmacokinetics of oral acetyl-L-carnitine in renal impairment

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Summary. Acetyl-L-carnitine 1.5 g and 3.0 g was administered as three divided doses on each of two occasions to 24 people with varying renal failure (creatinine clearance 127 – 8 ml · min^{-1}). Plasma and urinary concentrations of total-L-carnitine, free (non-esterified) carnitine, short-chain esters and acetyl-L-carnitine were measured.

The baseline (pre-study) concentrations of all four substances were related to renal function. Patients whose creatinine clearance was below about 30–40 ml · min^{-1} were had the highest concentrations.

Renal elimination of all four substances was related to dose and to renal function. There was evidence for dose-related elimination, with greater elimination of the larger dose.

Key words: Acetyl-L-carnitine, renal impairment; pharmacokinetics, adverse reactions

Acetyl-L-carnitine is a quaternary ammonium compound physiologically present in man. Carnitine acetyl transferase provides a dynamic equilibrium between L-carnitine and acetyl-L-carnitine, which may be biotransformed to acetylcholine. It has been suggested that administration of acetyl-L-carnitine to patients with deteriorating mental function may improve associative, cognitive and decisional processes [1–3]. Accordingly, this substance is of interest in the treatment and prevention of degenerative decreases in mental function, such as those related to dementia and ageing, possibly by an action on the cholinergic nervous system [4]. Since acetyl-L-carnitine may be administered to elderly people or those with other diseases, such as renal impairment, it is important to define its pharmacokinetics in renal impairment.

Materials and methods

Observations were made in 24 subjects, divided into four groups of 6.

Group 1: normal renal function, GFR (as creatinine clearance) greater than 90 ml · min^{-1} · 1.73 m^{-2}; Group 2: creatinine clearance 50–80 ml · min^{-1} · 1.73 m^{-2}; Group 3: creatinine clearance 20–50 ml · min^{-1} · 1.73 m^{-2}; and Group 4: creatinine clearance less than 20 ml · min^{-1} · 1.73 m^{-2}. Details of the individual subjects are shown in Table 1.

Study procedure

The study was approved by the appropriate Ethical Committee and all subjects gave their informed consent to it. There were two periods to the study. In period I subjects received acetyl-L-carnitine 1,500 mg in three divided oral doses of 500 mg at 08.00 h, 14.00 h and at 20.00 h. In period II subjects received acetyl-L-carnitine 3,000 mg in three divided oral doses of 1,000 mg at 08.00 h, 14.00 h and at 20.00 h. Fifteen days separated each period. Participants had fasted for a minimum of eight hours before beginning each period. Drugs were administered together with 150 ml water.

Table 1. Details of subjects

Group	Subject	Crcl ml · min^{-1}	Sex M/F	Age y	Weight kg	Height cm
1	JJ	127	M	27	80	170
	PM	126	M	26	90	195
	EB	124	M	24	78	192
	DC	118	M	24	64	173
	GR	108	M	30	74	175
	SL	96	M	29	74	175
2	JM	80	M	29	65	180
	JS	79	M	28	75	177
	EK	76	M	29	75	176
	SLY	74	M	23	86	185
	LT	70	M	61	66	170
	PMG	51	M	68	76	169
3	JC	47	M	55	104	185
	TR	36	M	52	72	170
	PS	36	M	64	72	172
	EP	35	F	23	60	166
	MH	32	M	19	75	173
	EMC	29	F	48	68	165
4	FB	18	M	71	68	162
	JK	18	M	54	78	178
	PB	16	M	44	82	180
	JKE	12	M	29	84	180
	AT	9	M	46	80	185
	RMG	8	M	47	74	175

Table 2. Mean (SEM) baseline plasma concentrations (nmol/ml) in the four groups prior to each study period

	Group	Period I	Period II
Total	1	50.5 (2.4)	53.9 (3.7)
	2	46.1 (6.7)	44.6 (5.4)
	3	112.6 (22.8)	83.6 (11.8)
	4	104.9 (14.3)	80.9 (5.0)
Free	1	45.8 (2.1)	48.4 (3.2)
	2	39.4 (4.3)	39.5 (4.4)
	3	92.3 (19.8)	69.0 (10.9)
	4	77.0 (9.6)	58.0 (3.8)
Short-chain	1	4.7 (1.3)	5.5 (1.3)
	2	6.7 (2.7)	5.1 (1.3)
	3	20.4 (3.9)	14.6 (1.8)
	4	27.9 (5.5)	22.9 (2.2)
Acetyl	1	2.2 (0.3)	2.1 (0.2)
	2	2.0 (0.5)	2.1 (0.5)
	3	5.4 (1.1)	4.9 (0.9)
	4	8.3 (2.6)	4.9 (1.0)

Table 3. Peak plasma concentrations (nmol/ml; m (SEM) during each study period

	Group	Period I	Period II
Total	1	57.44 (3.00)	63.5 (4.47)
	2	54.05 (8.24)	57.2 (6.78)
	3	145 (34.5)	105 (11.7)
	4	116 (15.5)	105 (9.79)
Free	1	52.0 (2.18)	57.0 (3.52)
	2	45.0 (5.64)	48.2 (4.72)
	3	118 (27.2)	85.4 (9.65)
	4	83.3 (9.85)	72.1 (7.21)
Short-chain	1	8.17 (0.82)	11.4 (1.58)
	2	11.4 (2.48)	11.3 (2.42)
	3	33.5 (6.95)	24.0 (4.01)
	4	39.4 (5.86)	37.07 (5.39)
Acetyl	1	4.20 (0.62)	4.50 (0.73)
	2	3.56 (0.88)	3.71 (0.95)
	3	8.57 (1.47)	6.67 (0.80)
	4	11.79 (3.06)	9.89 (2.15)

A 6 ml venous blood specimen was obtained from each subject at the following times after the first dose in each period: 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 and 48 h. Blood was collected in heparinized tubes, the plasma separated by centrifugation and stored at −20°C until assayed. Urine was collected over the following time intervals in each period: 0–4, 4–8, 8–12 and 12–24 h. Volume and pH were recorded and 5 ml aliquots stored at −20°C in the presence of sodium azide until required for assay.

Analytical methods

Concentrations of total L-carnitine, (free plus short-chain esters), free (non-esterified) L-carnitine, short chain carnitine esters and acetyl-L-carnitine were determined in neutralized perchloric acid extracts of plasma and urine by radioenzymatic methods [5–7]. The assay was linear over the range of concentrations encountered. Lower limits of quantitation for the purposes of the study were 10 nmol·ml^{-1} in plasma for total and free L-carnitine, 1 nmol·ml^{-1} for short-chain esters and 0.2 nmol·ml^{-1} for acetyl-L-carnitine. Inter-assay variability (coefficient of variation) for total L-carnitine was 7.9% at normal values (41 nmol·ml^{-1}, $n = 8$) and 9.1% at elevated values (220 nmol·ml^{-1}, $n = 8$). These figures are generally typical of the assay performance.

Numerical methods

Concentrations in plasma are given in nmol·ml^{-1}. Urinary elimination was calculated as the product of urinary volume and concentration and was converted to μmol eliminated in a given time. Renal clearance was calculated as the amount eliminated in the urine divided by the area under the plasma concentration-time curve (AUC) in the same time interval. AUC was calculated using the trapezoidal rule. Where not specified in the text, values are given as the mean and SEM. The significance of differences between means was calculated by parametric or non parametric methods, as described.

Results

There were no adverse clinical effects.

Plasma concentrations

Pre-dose plasma concentrations of all four substances tended to be higher in renal impairment (Table 2). In general, pre-dose concentrations were similar in Groups 1 and 2, suggesting that mild renal impairment had little effect. Whereas mean pre-dose concentrations were markedly higher in Groups 3 and 4, indicating that moderate-to-severe renal impairment had a large effect. Pre-dose concentrations were similar in both Periods I and II. For all four substances there was an inverse curvilinear relationship between pre-dose concentration and creatinine clearance, as illustrated for total acid-soluble carnitines in Fig. 1. The relationships were statistically significant (Spearman's rank correlation coefficient, $P < 0.01$). Values of this coefficient in the pre study Period I were: total – 0.728; free – 0.662; short-chain esters – 0.793; acetyl-L-carnitine – 0.643.

Following administration of acetyl-L-carnitine, the concentrations of all four substances were increased (Table 3). The increases tended not to be sharply defined and were not necessarily temporally relate to the dose of acetyl-L-carnitine. Rather, there was a slow increase in baseline concentrations over 24 hours, with some superimposed peaks. This is illustrated for short-chain esters and acetyl-L-carnitine in Fig. 2 and 3. For total and free carnitine, the increases were small in relation to the baseline concentrations.

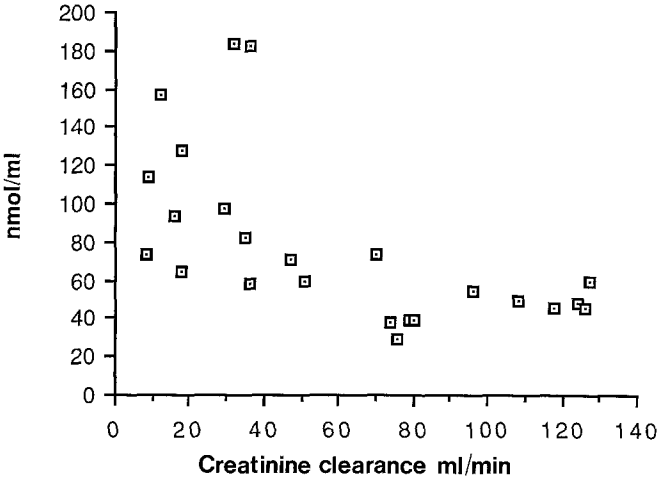

Fig. 1. Pre-treatment concentrations of total acid-soluble carnitines versus creatinine clearance

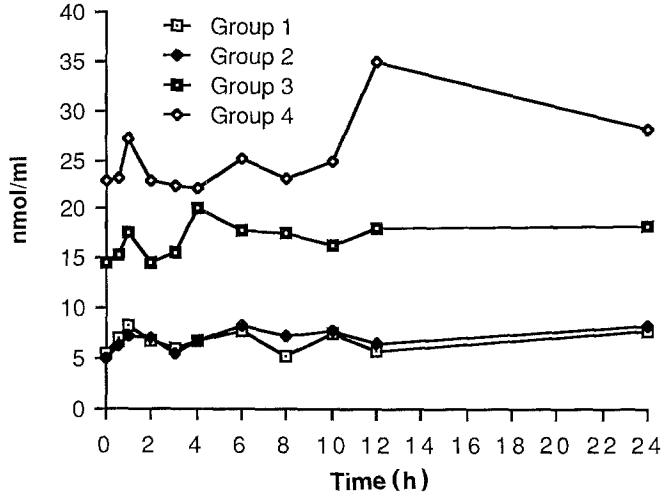

Fig. 2. Mean plasma concentrations of short-chain eslers (period 2)

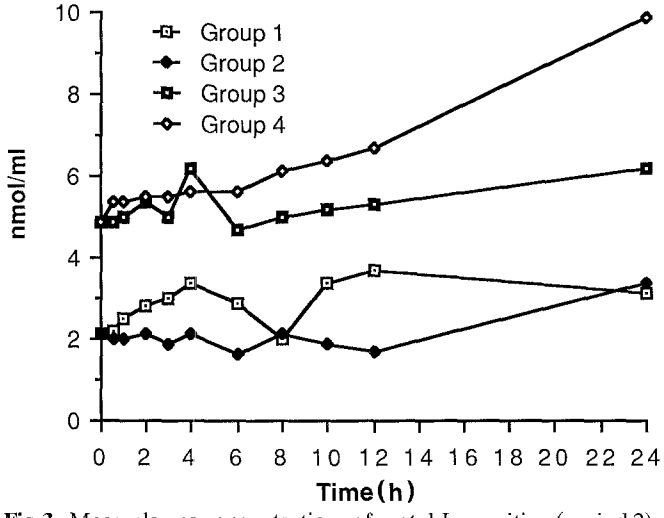

Fig. 3. Mean plasma concentrations of acetyl-L-carnitine (period 2)

Concentrations at 24 h were generally higher than at 0 h for all four substances, and at 48 h they were similar to those at 0 h. A notable finding was that even though the dose in Period II was twice that in Period I (3,000 mg total vs 1,500 mg total), the plasma concentrations of the four substances did not reflect that difference and the peak concentrations tended to be not greatly different during the two periods.

Urinary elimination

The mean 24 h urinary elimination of the four substances is shown in Table 4. Urinary elimination of all four substances was related to renal function, as it decreased with progressive renal impairment. Urinary elimination of each substance was higher after the larger dose. With the exception of the elimination of total and free carnitine during Period I, elimination of each substance was linearly related to creatinine clearance as follows:

Total, Period II, $r^2 = 0.41$, $P < 0.05$.
Free, Period II, $r^2 = 0.44$, $P < 0.05$.
Short-chain, Period I, $r^2 = 0.55$, $P < 0.01$.
Short-chain, Period II, $r^2 = 0.53$, $P < 0.01$.
Acetyl, Period I, $r^2 = 0.63$, $P < 0.01$.
Acetyl, Period II, $r^2 = 0.60$, $P < 0.01$.

The mean results for renal clearance are shown in Table 5. There were clear effects of renal function upon renal clearance of all four substances. Renal clearance decreased with progressive renal impairment. It was often higher after the larger dose of acetyl-L-carnitine. There was a significant linear relationship between renal clearance of all four substances and creatinine clearance, the correlation coefficients being:

Total,	Period I	$r^2 = 0.73$	$P < 0.001$
	Period II	$r^2 = 0.63$	$P < 0.001$
Free,	Period I	$r^2 = 0.47$	$P < 0.05$
	Period II	$r^2 = 0.59$	$P < 0.01$
Short chain,	Period I	$r^2 = 0.75$	$P < 0.001$
	Period II	$r^2 = 0.65$	$P < 0.001$
Acetyl,	Period I	$r^2 = 0.80$	$P < 0.001$
	Period II	$r^2 = 0.66$	$P < 0.001$

Table 4. Mean (SEM) 24 h urinary elimination (μmol)

	Group	Period I	Period II
Total	1	743 (92)	1130 (187)
	2	477 (74)	551 (125)
	3	686 (127)	731 (129)
	4	363 (84)	551 (172)
Free	1	390 (63)	778 (167)
	2	260 (77)	245 (80)
	3	501 (83)	458 (104)
	4	182 (53)	282 (97)
Short-chain	1	353 (38)	560 (115)
	2	289 (66)	306 (51)
	3	216 (30)	273 (35)
	4	179 (36)	229 (77)
Acetyl	1	137 (20)	115 (13)
	2	72 (27)	83 (15)
	3	62 (14)	88 (16)
	4	45 (13)	56 (16)

Table 5. Mean (SEM) renal clearance ($ml \cdot min^{-1}$)

	Group	Period I	Period II
Total	1	598 (75)	833 (141)
	2	443 (75)	478 (91)
	3	278 (67)	347 (59)
	4	163 (54)	267 (104)
Free	1	347 (54)	653 (144)
	2	270 (85)	243 (67)
	3	255 (46)	260 (46)
	4	110 (39)	200 (75)
Short-chain	1	2920 (496)	4100 (1170)
	2	2130 (624)	2040 (373)
	3	512 (184)	773 (189)
	4	315 (119)	440 (188)
Acetyl	1	2140 (266)	1810 (238)
	2	1200 (412)	1860 (465)
	3	527 (192)	723 (127)
	4	312 (134)	485 (195)

Discussion

In the present study, baseline concentrations of total, free, short-chain and acetyl-L-carnitine were higher in renal impairment. However, differences from healthy people were not large until creatinine clearance fell below about 40 ml/min when the concentrations increased rapidly with further falls in renal function.

Following administration of acetyl-L-carnitine, the increases in the plasma concentrations of all four substances were small, although as a rule they were larger with greater renal impairment. Peak concentrations of the four substances tended not to be notably different between the two doses of acetyl-L-carnitine, although the 24 h concentrations were more clearly related to the dose of acetyl-L-carnitine.

There were clear relationships between renal elimination of all four substances studied and renal function, measured as creatinine clearance. Renal clearance was high relative to glomerular filtration rate. Renal elimination in 24 h in most cases was linearly related to creatinine clearance, and renal clearance was significantly related to the creatinine clearance.

The fact that peak plasma concentrations did not notably increase with doubling of the dose, together with the tendency towards greater renal elimination and renal clearance at the higher dose, supports the concept of a renal threshold for carnitine and related substances [8, 9] as a mechanism aimed at preserving homeostatic equilibrium. Interestingly, even in Group 4, where individuals had creatinine clearance of $18\ ml \cdot min^{-1}$ or less, and where renal elimination of all four substances was low, they were able to increase both renal elimination and renal clearance in response to the larger dose.

In conclusion, renal function had effects on plasma concentrations and on urinary elimination of the four substances studied. The effects were proportional to renal function. There may be dose-related renal elimination of all four substances. Against the background of higher baseline plasma concentrations in renal impairment, the increases produced by the two dosing regimens were small, leading to the conclusion that the mechanisms allowing the body to preserve or restore homeostatic equilibrium of L-carnitine and related substances remains functional in patients with renal impairment.

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