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Pharmacokinetics of Bolus Intravenous and Oral Doses of L-Carnitine in Healthy Subjects

P. Harper[1], C.-E. Elwin[2], and G. Cederblad[1]

Departments of [1] Clinical Chemistry, Karolinska Institute, Danderyd Hospital, Danderyd and [2] Clinical Pharmacology, Karolinska Institute, Danderyd and Huddinge Hospitals, Huddinge, Sweden

Summary. The pharmacokinetics of single intravenous and oral doses of L-carnitine 2 and 6 g was studied in 6 healthy subjects on a low-carnitine diet. Carnitine was more rapidly eliminated from plasma after the 6 g dose. Comparing the doses, the $t_{1/2\beta}$ of the elimination phase (β) was 6.5 h vs 3.9 h, the elimination constant 0.40 vs 0.50 h^{-1} and the plasma carnitine clearance was 5.4 vs 6.1 $l \cdot h^{-1}$ for the 2 g and 6 g doses, respectively, showing dose-related elimination. Saturable kinetics were not found. The apparent volumes of distribution after the two doses were not significantly different and were of the same order as the total body water. Urinary recoveries of the 2 g and 6 g doses were 70% and 82%, respectively, during the first 24 h. Following the oral doses, there was no significant difference between the areas under the plasma carnitine concentration-time curves. Urinary recovery was 8% and 4% for the 2 g and 6 g doses during the first 24 h. Oral bioavailability was 16% for the 2 g dose and 5% for the 6 g dose. The results suggest that the mucosal absorption of carnitine was already saturated by the 2 g dose.

Key words: L-carnitine; pharmacokinetics, intravenous and oral doses, bioavailability, healthy volunteers

Carnitine, 3-hydroxy-4-N-trimethylammonium butyrate, is an endogenous substance whose last biosynthesis step in man occurs in the liver and kidneys [1]. Over 90% of the body carnitine is found in skeletal and cardiac muscle [2]. L-carnitine is an essential cofactor in β-oxidation of longchain fatty acids. Evidence for other functions as well has been produced in recent years [3].

Since the first description of a patient with primary carnitine deficiency in 1973, several cases of primary genetic carnitine deficiency syndromes have been reported, as well as more cases of secondary carnitine deficiency syndromes [4]. The need to prevent and treat carnitine deficiency has become clear. Although carnitine is being administered to an increasing number of patients to investigate its therapeutic potential, its pharmacokinetics has not been extensively studied. An open two-compartment model was employed to study carnitine pharmacokinetics after intravenous administration of DL-carnitine to patients with coronary heart disease [5] and after a bolus dose of a fat emulsion and L-carnitine in healthy subjects [6]. After oral L-carnitine, the maximum increase in plasma carnitine was observed after several hours [7]. In another study, oral administration of L-carnitine to healthy fasting individuals showed that 10% of the dose was excreted in the following 6 h [8]. Experimental studies in rats have been conclusive in demonstrating that the uptake of both the isomers L- and D-carnitine by the intestinal mucosa is a saturable process [9]. This has not been evaluated in man.

The aim of the present study was to describe the basal pharmacokinetics of L-carnitine after intravenous and oral bolus doses at two levels in healthy subjects, and so also to investigate the oral bioavailability of carnitine. The subjects were put on a low-carnitine diet to reduce the influence of exogenous carnitine [10].

Materials and Methods

Subjects

Volunteers were considered healthy according to medical records, physical examination and routine blood tests, and they were not receiving any drugs except for one individual who was euthyroid on thyroxine substitution. Six women participated in

both periods of the study. Their mean age was 38 y (range 29–46 years), and mean weight 60 kg (range 54–77 kg). Informed consent was obtained and the subjects were fully informed about the purpose of the study and the substance they would receive. The study was approved by the Ethics Committee of the Karolinska Institute.

Study Design

The study was carried out in two 9 day periods, at least one month apart, involving two different doses of L-carnitine. Each period consisted of an intravenous and an oral phase. The substance given was L-carnitine, the inner salt (Sigma-Tau, Rome, Italy), 1 g ampoules for intravenous use and 0.33 g tablets for oral use. The subjects were placed on an ovovegetarian diet throughout each nine day period. On the fifth day the intravenous dose was given and on the seventh day the oral dose.

At 7–8 a.m. a short catheter was inserted percutaneously into an antecubital vein in one arm. The catheter was flushed with saline solution. Heparinized venous samples were obtained prior to injection or ingestion of the dose, intermittently for up to 12 h and again 24 h after administration. Blood samples were also obtained after 48 h when the higher doses were given. Urine was collected as 24 h samples during the nine days.

L-Carnitine 2 g (12.4 mmol) and 6 g (37.2 mmol), respectively, was given as an intravenous bolus injection after a 12 h fast. The doses were administered in the contralateral arm over 4 and 10 min, respectively. The sample time clock was started halfway through the infusion. The oral dose was given 1 h after a light breakfast. The 2 g dose was taken with 100 ml water and the 6 g dose with 400 ml.

Analytical Methods

Heparinized whole blood was promptly centrifuged at 3000 *g*, at room temperature, and the plasma was stored at −20° C until analyzed. The urine samples, collected in bottles containing 5 ml thymol-isopropanol solution [11] as preservative, were stored at −20° C until analyzed.

Total carnitine in plasma was assayed radioenzymatically [12, 13]. Total carnitine in urine was assayed by a spectrophotometric method adapted to the Cobas Bio centrifugal analyzer [14]. The coefficient of variation of the plasma total carnitine analysis was 4.1% (mean = 47.0 μmol/l, $n=23$) for the radioenzymatic method, and 5.5% (mean = 58.0 μmol/l, $n=24$) for the spectrophotometric method. Creatinine in plasma and urine were analyzed by routine laboratory methods based on the picrate reaction.

Pharmacokinetic Analysis

Plasma carnitine concentrations were analysed as a function of time after the bolus intravenous injection of carnitine using an open two-compartment model. The pharmacokinetic constants were calculated with a computer program [15] based on the following equation

$$C_t = A_e^{-\alpha t} + B_e^{-\beta t}$$

where C_t is the plasma carnitine concentration at any time t. A and B are the extrapolated intercepts at zero time of the fast and slow exponential components, respectively, and α and β are their slopes. The rate constants k_{12}, k_{21} and k_{el} were also obtained from the same program. The plasma half-life of distribution ($t_{1/2\alpha}$) and of elimination ($t_{1/2\beta}$) were calculated as $\ln 2/\alpha$ and $\ln 2/\beta$.

The areas under the plasma carnitine concentration-time curves (AUC) after i.v. and oral administration were estimated by the trapezoidal rule. The AUC was also calculated by $AUC = A/\alpha + B/\beta$. The plasma carnitine clearance (CL) and the apparent volume of distribution (V_z) were calculated by routine pharmacokinetic formulae [16]. Oral bioavailability (f) was calculated after subtraction of the individual basal carnitine concentrations from all values.

The renal clearance (CL_R) of i.v. carnitine was calculated as the total amount of carnitine excreted in the urine over 24 h divided by AUC (0–24), and over 48 h divided by AUC.

Endogenous creatinine and basal carnitine renal clearances were also calculated on the fourth day after starting the ovovegetarian diet.

Urinary recovery of carnitine was calculated as the ratio between carnitine excreted in the 24 or 48 h after the intravenous dose and the amount given.

Statistical Analysis

Paired Wilcoxon and Student's *t*-tests were used for comparison between groups.

Results

Influence of Diet on Carnitine Excretion

After the start of the ovovegetarian diet, the mean values (± SEM) of urinary carnitine were 228 ± 36,

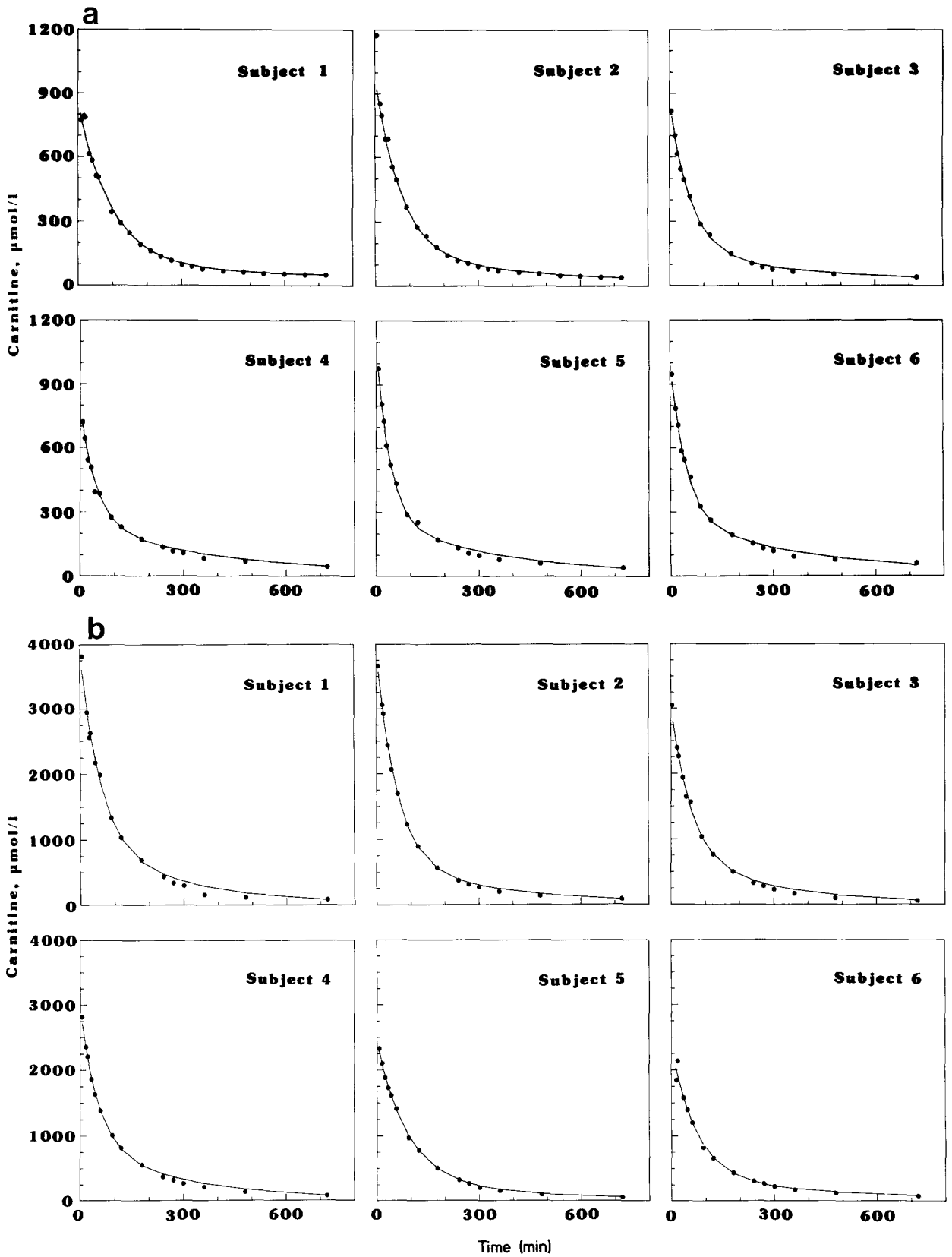

Fig. 1a, b. Individual plasma carnitine concentration-time curves after intravenous administration of 2 g **a** and 6 g **b** L-carnitine. The *dots* correspond to actual plasma carnitine concentration obtained and the line to the computer fit

Table 1. Pharmacokinetic data for 2 g and 6 g L-carnitine given intravenously

		2 g, $n=6$ mean ± SD		6 g, $n=6$ mean ± SD		Sign[a] P
Body weight	(kg)	60	9	60	9	
A	($\mu mol \cdot l^{-1}$)	741	103	2414	515	
α	(h^{-1})	1.087	0.327	0.980	0.181	
$t_{1/2\alpha}$	(h)	0.69	0.23	0.73	0.15	NS
B	($\mu mol \cdot l^{-1}$	193	71	692	266	
β	(h^{-1})	0.119	0.036	0.183	0.034	
$t_{1/2\beta}$	(h)	6.48	2.79	3.92	0.83	<0.05
k_{12}	(h^{-1})	0.468	0.170	0.301	0.084	NS
k_{21}	(h^{-1})	0.334	0.155	0.364	0.108	NS
k_{el}	(h^{-1})	0.401	0.065	0.497	0.047	<0.05
AUC[b]	($\mu mol \cdot h \cdot l^{-1}$)	2358	318	6187	854	
AUC[c]	($\mu mol \cdot h \cdot l^{-1}$)	2372	382	5964	777	
Infinite area[d]	%	17	7	7.1	2.7	
CL	($l \cdot h^{-1}$)	5.37	0.70	6.08	0.80	<0.025
V_z	(l)	48.3	13.8	34.9	11.1	
V_z	($l \cdot kg^{-1}$)	0.82	0.29	0.58	0.15	NS

[a] Wilcoxon matched-pairs test for comparison of the 2 g and 6 g doses
[b] $AUC = A/\alpha + B/\beta$
[c] AUC = area by trapezoidal rule + C_{tn}/β
[d] of the area according to c

Table 2. Urinary carnitine excretion, basal and after intravenous administration of L-carnitine

Subject	Creatinine clearance[a] ($ml \cdot min^{-1}$)	Renal carnitine clearance[a] ($ml \cdot min^{-1}$)	Renal carnitine clearance 24 h urine/AUC (0-24)[bc] ($ml \cdot min^{-1}$)		Renal carnitine clearance 48 h 48 h urine/AUC[bd] ($ml \cdot min^{-1}$)		Urinary recovery of carnitine 24 h urine[b] (%) of dose	
			2 g	6 g	2 g	6 g	2 g	6 g
1	79	2.3	74	69	50	70	72	76
2	74	1.7	60	86	63	82	71	83
3	72	3.4	89	108	73	100	70	87
4	68	2.4	75	100	64	89	66	82
5	97	4.1	94	101	76	94	76	77
6	91	4.4	74	137	59	112	66	89
Mean	80	3.1	78	100	64	91	70	82
± SD	11	1.1	12	23	9	14	4	5
Sign[e]			NS		$P<0.05$		NS	

[a] Endogenous creatinine and basal carnitine renal clearance on the fourth day after dietary change using the following formula $CL = (U \times V)/P$
[b] Basal urine carnitine values (Day 4) subtracted
[c] AUC (0-24) according to the trapezoidal rule. Basal plasma carnitine values subtracted
[d] AUC is according to the equation $A/\alpha + B/\beta$
[e] Paired Student's t-test, $n=6$

185 ± 32, 152 ± 28, 108 ± 21 μmol/24 h for the 2 g pre-dose period, and 193 ± 55, 158 ± 37, 157 ± 45, 116 ± 14 μmol/24 h for the 6 g period.

One subject put on an ovovegetarian diet collected urine for 10 days. The consecutive carnitine values in her urine were 233, 202, 169, 105, 96, 92, 85, 65, 72 and 102 μmol/24 h.

Intravenous Administration

Plasma carnitine concentration-time curves are shown in Fig. 1. For each individual and dose the actual plasma concentrations obtained (dots) and the corresponding computer fit (line) are illustrated. The pharmacokinetic data are listed in Table 1. The

intercepts A and B and the AUC were proportional to the dose of carnitine. There was no significant difference between the half-lives of the distribution phase ($t_{1/2\alpha}$) for the two doses. The plasma half-life of the elimination phase ($t_{1/2\beta}$) was shorter after the 6 g dose ($p<0.05$). The elimination constant (k_{el}) was larger with the 6 g dose ($p<0.05$) and the plasma clearance (CL) was higher ($p<0.025$). Although not statistically significant, the mean apparent volume of distribution (V_z) after the higher dose was smaller than after the lower dose.

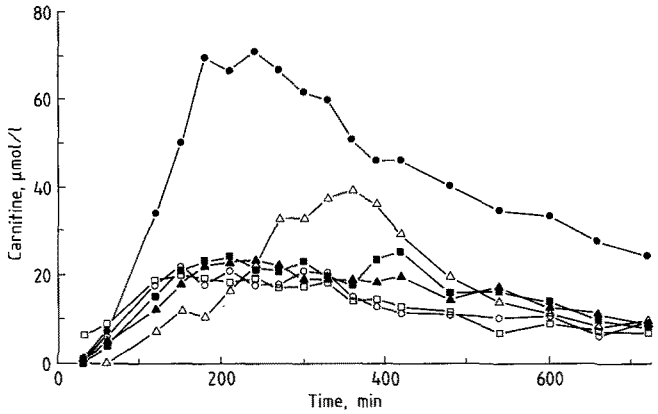

Fig. 2. Plasma carnitine concentration-time curves after oral administration of 2 g L-carnitine

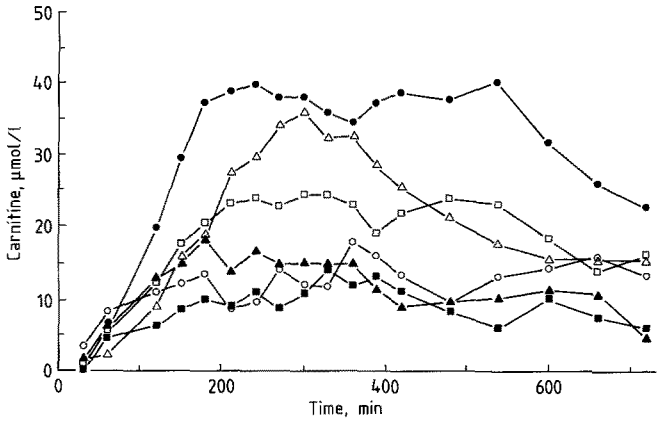

Fig. 3. Plasma carnitine concentration-time curves after oral administration of 6 g L-carnitine

Urinary carnitine before and after the intravenous doses are summarized in Table 2. CL_R during the 48 h after injection was greater for the 6 g than for 2 g dose ($p<0.05$).

The mean 24 h urinary recovery after the 2 and 6 g doses were 70±4 (SD) % and 82±5%, respectively, (Table 2). The corresponding values after 48 h urine collection added little, mean (±SD) 74±6% and 86±6%, respectively. There was no significant difference between the doses in the urinary recovery of carnitine over 24 or 48 h expressed as % of the dose.

Two subjects suffered from side-effects after 6 g i.v. One complained of headache, feeling faint and visual blurring for a few minutes. The other complained of visual blurring under the same circumstances. These side effects of intravenous carnitine appear not to have been previously described.

Oral Administration

The plasma carnitine concentration-time curves after oral administration of carnitine are shown in Figs. 2 and 3. There was no significant difference between the AUCs of 2 g and 6 g doses (Table 3). The bioavailability of the oral 2 g dose ranged from about 9% to 25%, and the corresponding values for the 6 g dose were lower, ranging from about 4% to 10%.

Of the 2 g and 6 g L-carnitine ingested,

Table 3. Oral bioavailability (f) of L-carnitine after 2 g and 6 g doses

Subjects	2 g						6 g					
	AUC (0-12)[a]			AUC (0-24)[a]			AUC (0-12)[a]			AUC (0-24)[a]		
	p.o.	i.v.	f[b]	p.o.	i.v.	f[b]	p.o.	i.v.	f[b]	p.o.	i.v.	f[b]
1	131	1710	0.08	183	2004	0.09	178	6287	0.03	254	6828	0.04
2	359	1731	0.21	483	1964	0.25	482	5938	0.08	680	6621	0.10
3	234	1392	0.17	357	1603	0.22	203	4961	0.04	288	5430	0.05
4	143	1509	0.10	240	1795	0.13	150	5072	0.03	230	5531	0.04
5	100	1516	0.07	151	1675	0.09	189	4664	0.04	233	5092	0.05
6	216	1564	0.14	384	1848	0.21	150	4029	0.04	194	4430	0.04
Mean	197[c]	1570	0.13[d]	300[c]	1815	0.16[d]	225[c]	5159	0.05[d]	313[c]	5656	0.05[d]
±SD	94	129	0.05	129	157	0.07	128	830	0.02	182	916	0.02

[a] AUC = Area under the plasma concentration-time curve, $\mu mol \cdot h \cdot l^{-1}$, basal carnitine values subtracted
[b] Oral bioavailability (f) = AUC (0-t) p.o./AUC (0-t) i.v.
[c] No significant difference was found between AUC p.o. of 2 g and 6 g doses
[d] Significant difference in bioavailability (f) for 2 g and 6 g doses, $P<0.01$

1021 ± 727 μmol ($\bar{x}$ ± SD) and 1580 ± 731 μmol were excreted in the following 24 h (basal values were subtracted), i.e. 8% and 4% of dose, respectively. In the next 24 h a further 1-2% was recovered in urine.

Discussion

Normal subjects eating a low-carnitine diet showed a decrease in urinary carnitine excretion, which reached about 110 μmol/24 h on the fourth day after the dietary change. These results are in accordance with those of Rudman et al. [10].

The pharmacokinetic data obtained from the computer program were compared with the other methods of calculating the AUC and showed good agreement; see Table 1.

The pharmacokinetics of carnitine did not show saturable kinetics after either of the intravenous doses. This conclusion is based on the observations that the half-lives of the distribution phase ($t_{1/2\alpha}$) were the same for both doses, and that the intercepts A at time zero and the total AUCs were proportional for the two doses.

After intravenous administration of carnitine, its plasma elimination rate was higher following the 6 g dose, since CL was higher, k_{el} was larger and $t_{1/2\beta}$ was shorter. This shows dose-related elimination of carnitine.

The kidneys are the major route of elimination of carnitine. The mean 24 h urinary recovery was 70 ± 4% (SD) for the 2 g dose (12.4 mmol), which is in agreement with the 75-80% obtained by Welling et al. [5], who gave 40 mg/kg DL-carnitine HCl, corresponding to a total mean dose of L-carnitine of 8.1 mmol. The recovery range, 66-76%, was smaller here than in that study, 12-127%. The discrepancy might be explained by the fact that the exogenous intake of carnitine here was minimized by use of a low-carnitine diet. Furthermore, L-carnitine was administered and it has been demonstrated that D-carnitine interferes with the renal excretion of L-carnitine [9].

The renal clearance of carnitine was found to be 20 to 30 times higher after the 2 g and 6 g doses than under basal conditions, i.e. on comparison with the fourth day after the dietary change and with values reported for healthy women, 4.9 ± 2.0 ml/min; [17]. The renal clearance of carnitine in the 24 h after the i.v. doses was in the range of the values obtained for creatinine clearance. This suggests that carnitine is readily filtered through the glomeruli and that the high tubular reabsorption capacity proposed for free L-carnitine [8] is saturated.

(V_z) of carnitine was of the same order as total body water volume, although it did show marked intersubject variation. This result should be interpreted with caution due to the limitations inherent in the (V_z) concept, and to the fact that carnitine is an endogenous substance with different uptakes and concentrations in various tissues. However, this finding indicates that carnitine is distributed in body fluids as an unbound solute. With current knowledge it is not possible to conclude if its extensive distribution both in extra- and intracellular water is of any significance for the proposed carrier and transport systems. Several authors have proposed carriermediated transport against concentration gradients for carnitine in the liver and in cardiac and skeletal muscle [18].

The term "bioavailability" refers to the proportion of a drug which reaches the systemic circulation unchanged after a particular route of administration. Several factors contribute to the low bioavailability found for carnitine, almost all of which have been studied in animals. In rats, it has been unequivocally shown that carnitine is degraded by the endogenous bacterial flora in the gastrointestinal tract, as metabolites have been found in conventional but not in germ-free rats [19, 20]. When a high dose (124 μmol) of radioactive L-carnitine was given orally, 23% of the dose was identified as trimethylamine-N-oxide (primarily in urine), and 31% as γ-butyrobetaine (primarily in faeces). About 30% of the dose was excreted as carnitine in conventional rats in contrast to 99% in germ-free rat (57% of the total dose was found in faeces).

No statistically significant difference was found here between the areas under the plasma carnitine concentration-time curves when oral 2 g or 6 g doses were given. This suggests that carnitine absorption was already saturated at the 2 g dose. This is in agreement with animal experiments, where carnitine was shown to be absorbed in the intestine by a partially saturable process [9, 21]. The uptake of L-carnitine was reduced from 78 to 6% when the dose was increased from 2.3 nmol to 288 μmol [9].

In the present study, the individual maximum carnitine concentrations in plasma were seen after 3-9 h and 2.5-7 h after the 2 g and 6 g doses, respectively. Bach et al. [7] gave a single 2 g dose of L-carnitine to 12 volunteers and found an increase in plasma carnitine of 57%, with a peak after 3.5 h. The delayed appearance of carnitine in the systemic blood stream agrees with the findings in animals. The uptake of carnitine by intestinal mucosal cells has been shown to be a slow process. The peak of radioactivity in intestinal tissue occurred 1-2 h after an intraluminal dose of L-carnitine [9, 22], and

radioactivity was then slowly released from the mucosal tissue. In one experiment 31% of the dose remained at 4 h and in another 46% at 5 h [9]. The appearance of radioactivity in the systemic circulation after intraluminal L-carnitine was very slow and was still increasing in experiments followed for 3 h [22] and 8 h [21].

Before reaching the systemic circulation, portal blood passes through the liver and this first passage is also a factor determining bioavailability. Radioactivity in the liver of the rat increased to 8% of the administered dose after 6 h, which may represent uptake both from the portal and the systemic blood flow [22]. It is not known whether this also occurs in man.

The present results also suggest that therapeutic intravenous administration of carnitine might preferably be given as a low dose infusion rather than as a rapid bolus injection. There does not appear to be any advantage in giving a dose larger than 2 g orally.

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Dr. Gitten Cederblad
Department of Clinical Chemistry
Huddinge Hospital
S-14186 Huddinge, Sweden