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Pharmacokinetics and Safety of l-Carnitine Infused I.V. in Healthy Subjects

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Summary. The pharmacokinetics and safety of a brief i.v. infusion of l-carnitine 0, 20, 40 and 60 mg/kg have been investigated in 10 healthy subjects.

The diurnal intraindividual variability of plasma carnitine was small (C.V. = 3.0, 3.9 and 3.9%, respectively), and the total 24 h excretion in urine was also small and relatively constant: 4.6, 21.5 and 13.0 mg/day in the controls vs 4.6, 20.2 and 6.0 mg/day during treatment in the three subjects to whom saline alone was administered according to a single-blind design. Therefore, the pre-dose level of carnitine was subtracted from the level after dosing for the pharmacokinetic analysis. Plasma carnitine fitted well to a three-compartment open model, with Vc of 0.11-0.20 l/kg and a $t_{1/2\gamma}$ of 10-23 h. The urine recovery in 24 h was 77.2-95.4%.

There were no objective or subjective side-effects attributable to carnitine, so its i.v. infusion is considered to be safe.

Key words: carnitine; i.v. infusion, pharmacokinetics, healthy subjects

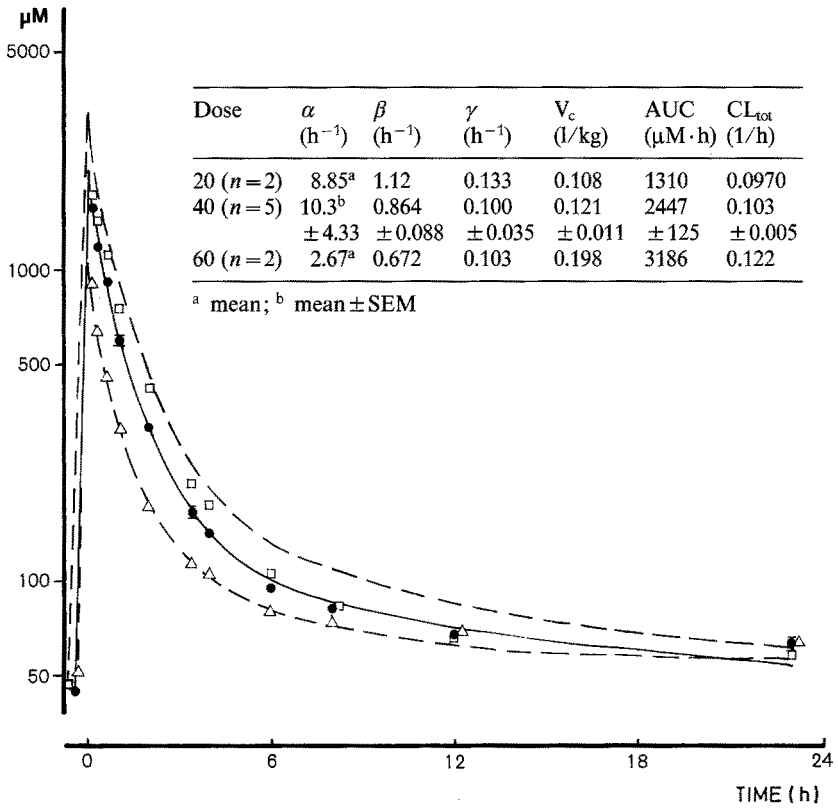
l-Carnitine occurs naturally in cardiac and skeletal muscle in man. It is required for the translocation of long-chain acyl CoA, a metabolic intermediate of fatty acids, into mitochondria [1, 2]. In the ischaemic heart, where l-carnitine is deficient, long-chain acyl CoA accumulates and is harmful to the ischaemic myocardium [3]. An exogenous supply of carnitine might have some beneficial effect in such hearts [4]. It has been shown in humans that intravenous administration of dl-carnitine to patients with angina pectoris was associated with an increase in tolerance of rapid cardiac pacing [5], and carnitine treatment in patients with cardiomyopathy has improved mechanical function [6].

The pharmacokinetics of l-carnitine after i.v. infusion of dl-carnitine have been reported elsewhere [7]. Although the *dextro-isomer* is not enzymatically esterified by mammals, and has been shown to have little or no effect on the overall pharmacokinetics of l-carnitine in dogs [6], investigation of the pharmacokinetics of l-carnitine after its sole administration appeared desirable to aid precise analysis. Because it occurs endogenously, carefully controlled conditions would have to be maintained during determination of the pharmacokinetic parameters. The present study comprised an assessment of the pharmacokinetics and safty of intravenous l-carnitine in healthy subjects.

Materials and Methods

Study Design

Ten healthy male subjects, aged 22-39 (mean 29.5) y, weighing 58.0-85.0 (mean 68.3) kg, participated in the study after giving their written informed consent to it. In the first period of study 3 out of 5 subjects were allocated to placebo and 2 to receive 20 mg/kg carnitine i.v. over 10 min, according to a single-blind design. In the second period carnitine 40 mg/kg was administered over 10 min to the remaining 5 subjects. In the third period 60 mg/kg carnitine was administered over 30 min to 2 of the 3 subjects who had received placebo in the first period. The higher dose was only given after the safety of the previous dose had been demonstrated. In the first and second periods the profile of excretion of carnitine in urine prior to and after the administration was determined using urine samples collected from



Dose	α (h^{-1})	β (h^{-1})	γ (h^{-1})	V_c (l/kg)	AUC (μM·h)	CL_{tot} (1/h)
20 ($n=2$)	8.85[a]	1.12	0.133	0.108	1310	0.0970
40 ($n=5$)	10.3[b]	0.864	0.100	0.121	2447	0.103
	±4.33	±0.088	±0.035	±0.011	±125	±0.005
60 ($n=2$)	2.67[a]	0.672	0.103	0.198	3186	0.122

[a] mean; [b] mean ± SEM

Fig. 1. Plasma concentration of carnitine following a brief i.v. infusion. *Ordinate:* concentration of carnitine in μM. *Abscissa:* time in h. Time 0 was the time of cessation of the carnitine infusion. Symbols (●) and bars show the mean ± SEM ($n=5$) of carnitine concentration after 40 mg/kg given in 10 min. The concentrations from each subject were fitted to a three-compartment model and the pharmacokinetic parameters were calculated. Using the means of those parameters the curves were simulated for 40 mg/kg (—) and for 20 mg/kg and 60 mg/kg (– –). Symbols (△ and □) show the means of measured values ($n=2$) after the 20 mg/kg and 60 mg/kg doses, respectively

−24-0, 0-2, 2-4, 4-6, 6-8, 8-12 and 12-24 h; the time of cessation of infusion was 0 h. In the third period urine was collected from −0.5-2, 2-8 and 8-24 h. Blood samples 7 ml were taken from each subject before, 0.083, 0.25, 0.5, 1, 2, 3.5, 4, 6, 8, 12 and 23 h after the end of infusion, centrifuged immediately and the plasma separated. Plasma and aliquots of urine were stored at −20 °C until analysed.

Standardized meals of 2100 kcal, providing 91 g protein, 34 g fat and 360 g carbohydrate per day were taken during each experimental period.

Determination of Carnitine in Plasma and Urine

Urine samples were eluted through a column containing an ionexchange resin (Dowex1-X4) before analysis. Free carnitine in plasma and urine was determined enzymatically by a modification of the method of Marquis and Fritz [8]. Although both unchanged carnitine and norcarnitine can be detected using this method [9], the latter has never been found in specimens from man [10], so it was considered that only carnitine would be determined. The lowest detection limit was 11 μM. Each sample was measured in triplicate and the coefficient of variation (C.V.) of measurements ranged from 0.4 to 4.4%.

Clinical Assessment

Blood pressure and pulse rate were measured at the same times as blood was sampled. A Holter ECG was recorded from before till 4 h after dosing in the first and second periods, and twelve lead ECGs were recorded before, 1 and 23 h after administration in all periods.

Drug

l-Carnitine (M.W. 161.2) was prepared as a 10% injectable solution by the Earth Chemical Co., Ltd. (Hyogo, Japan) and was further diluted with saline.

Data Analysis

Plasma carnitine concentrations were fitted to a pharmacokinetic model by a non-linear least squares method, using the microcomputer program MULTI [11].

Results

Plasma carnitine concentrations after placebo in three subjects, at 12 time-points within 23 h, were 37.2 ± 1.1, 44.5 ± 1.7 and 41.8 ± 1.6 μM (mean ± SD), respectively. This means that the intraindividu-

Table 1. Excretion of carnitine in urine

Dose (mg/kg)	mg/man	*n*	Excretion in urine (mg)								Recovery in 24 h (%)
			−24–0 h	0–2 h	2–4 h	4–6 h	6–8 h	8–12 h	12–24 h	0–24 h	
0		3	13.0 ±8.5	2.0 ±1.6	1.1 ±0.8	1.1 ±0.8	1.1 ±0.4	1.6 ±1.3	3.4 ±4.0	10.3 ±8.6	
20	1360	2	16.6	832	149	55.8	36.1	28.0	55.1	1160	83.8
	1300		31.0	1000	129	47.3	27.1	25.1	42.5	1270	95.4
40	2940 ±368	5	13.2 ±9.4	1660 ±186	335 ±103	132 ±32.5	64.3 ±12.4	71.6 ±12.0	121 ±37.8	2390 ±322	80.8 ±4.3
60	3600	1	13.0[a]	2470[b]		545.3			62.9	3080	85.2

Values in the cases of 0 mg/kg and 40 mg/kg are expressed as mean ± SD; [a] this was the value prior to administration of placebo (0 mg/kg); [b] −0.5–2 h

al variability of plasma carnitine within a day was 3.0, 3.9 and 3.9% expressed as the C.V., which was within the range of measurement error. Therefore, in each individual the pre-dose plasma carnitine was subtracted from the levels after administration for pharmacokinetic analysis. The data fitted better to a three-compartment open model than to a two-compartment model, with a lower AIC (Akaike's information criterion) value [12]. The data are summarized in Fig. 1.

The excretion profile of carnitine in urine is shown in Table 1. Carnitine was detected in urine on the day before dosing, but the amount was very small compared to that recovered after dosing and it was constant between days: 4.6, 21.5 and 13.0 mg/day in the control period vs 4.6, 20.2, 6.0 mg/day during administration, respectively, in the three subjects given a placebo infusion. Therefore, the amount of carnitine excreted on the control day was subtracted from that in the corresponding block sample on the day of administration. In the case of administration of 20 mg/kg and 40 mg/kg, 50–75% was recovered in urine by 2 h, 70–90% by 8 h and 75–95% by 24 h after dosing. In total a mean of 83.5% was recovered in 24 h.

No abnormality attributable to the agent was found in subjective symptoms, physical findings, blood pressure, 12-lead ECGs or Holter ECGs.

Discussion

l-Carnitine occurs endogenously, it is also found in food, especially in meat and fish [13], and it is present in human plasma and urine even without an exogenous supply. On a standardized diet, the intra- and interindividual variability of the plasma concentration and excretion rate of carnitine were small compared to the amount administered. Intravenous carnitine was well tolerated and its disappearance from plasma followed a three-compartment open model. Welling et al. [6] used a two-compartment open model to fit the plasma l-carnitine levels after i.v. injection of dl-carnitine, which they measured only at 7 time-points for 12 h after dosing. In the present study the time profile of l-carnitine level in plasma was apparently better fitted by a three-compartment open model, which gave a smaller AIC value than a two-compartment model. The volume of distribution of the central compartment (V_c) was about 0.11–0.20 l/kg and corresponds to extracellular fluid volume. Carnitine infused into the blood was distributed into two peripheral compartments. The half-life of the gamma phase of disappearance ($t_{1/2\gamma}$) was about 10–23 h. Of the administered carnitine 77.2–95.4% was recovered in the urine by 24 h. A subject who took 60 mg/kg carnitine showed the lowest recovery (57.8%), but that could be attributed to a possible error in urine sampling and the data were excluded from the analysis, even though there might have been large interindividual variability in urine excretion. Although the peak concentration of carnitine following infusion of 40 mg/kg in 10 min reached 1612.3 μM (about 36-times the pre-dose value), the dose was well torelated and there were no subjective or objective side-effects.

In conclusion, the i.v. administration of carnitine appears to be safe, and its pharmacokinetics can be analysed just by knowing the pre-dose level in plasma.

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