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# Kinetics of intravenously administered carnitine in haemodialysed children

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**Abstract**: The pharmacokinetics of low-dose bolus L-carnitine (5 mg $kg^{-1}$ body wt) in five haemodialysed children were investigated. Kinetic variables were obtained by applying a two-compartment open model. The elimination half-life was very short, 2.43 ± 0.35 h, despite the reduced plasma clearance of 41.2 ± 5.7 ml $min^{-1}$, compared with healthy adults. The apparent volume of distribution, 0.27 ± 0.07 l $kg^{-1}$ body wt, corresponds well to the size of the extracellular space. The kinetic behaviour of intravenously supplied carnitine may assist in future evaluations of the therapeutic application of this drug in uraemic children.

**Keywords**: *L-Carnitine; haemodialysis; paediatrics; chronic uraemia; pharmacokinetics.*

## Introduction

Carnitine (3-hydroxy-4-*N*-trimethylaminobutyric acid) is a naturally occurring compound, that transports long-chain fatty acids across the inner mitochondrial membrane thereby facilitating β-oxidation [1]. By the action of the carnitinepalmitoyl-transferase I palmitoyl-CoA reacts with carnitine giving palmitoylcarnitine and CoA. Palmitoylcarnitine is then transported over the inner membrane, the transport being catalysed by the carnitine carrier. In the mitochondrial matrix, palmitoylcarnitine is reconverted into palmitoyl-CoA, catalysed by carnitinepalmitoyltransferase II. As fatty acids are the main substrates for energy production in skeletal and heart muscle, adequate concentrations of carnitine are required for normal fatty acid oxidation in these tissues.

In chronic uraemic patients undergoing regular haemodialysis treatment, the plasma free concentration of carnitine is considerably decreased while that of acylated carnitine is markedly increased [2, 3]. Therefore uraemic hypertriglyceridemia has been claimed to emerge partly due to the reduced amount of free carnitine [4], and thus supplementary therapeutical application has been proposed [5–12].

The pharmacokinetic properties of intravenously administered carnitine have only been described in healthy adults. In these studies, the apparent volume of distribution was assumed to be about 26% of the body weight. The kidneys are the major route of elimination of carnitine. Following an intravenous injection 80% has been recovered in the urine within 24 h [13–15]. The rate of disappearance of carnitine was characterized by a half-life of 1.5–3 h [14, 15]. The present investigation is the first trial to deal with the pharmacokinetic characterization of carnitine in uraemic children. The study was designed to evaluate the kinetic behaviour of L-carnitine after bolus injection in haemodialysed children with type IV hyperlipoproteinaemia.

## Experimental

### *Patients*

Five haemodialysed children (mean age: 14.4 ± 3.4 years; mean body wt: 34.4 ± 6.9 kg; renal creatinine clearance <5 ml $min^{-1}$) were studied after an overnight fast. None of the patients had finished puberty and they were in stable clinical condition. The investigations were performed on days without haemodialysis treatment under body rest. Informed consent was obtained from the parents and the study protocol was approved by the ethical committee of the University of Münster.

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*Experimental and analytical procedure*

All patients were given a bolus injection of L-carnitine (Biocarn®, Nephro-Pharma, Bad Aibling, FRG) at a dose of 5 mg (31 μmol)/kg body wt. The bolus injections were accomplished within 1–2 min. On 11 occasions over 180 min, blood samples were drawn via a catheter placed in an antecubital vein, before and immediately after the bolus injection, into EDTA-tubes. The sampling times were 4, 8, 12, 20, 30, 60, 90, 120, 150 and 180 min after the bolus. Blood specimens were immediately centrifuged (200 ***g*** for 10 min) and the plasma stored at −70°C until analysis.

Plasma concentrations of total carnitine (TC), free carnitine (FC), short-chain acylcarnitine (SCC) and long-chain acylcarnitine (LCC) were assayed using a modified radiochemical enzymic method [16].

*Kinetic evaluation*

A two-compartment open model was applied and standard equations and symbols were used as recommended by Aronson *et al.* [17]. Kinetic calculations were carried out by employing a BASIC computer program, PKCALC [18], based on the following equation:

$$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_z t}.$$

Plasma half-life of distribution ($t_{½}\lambda_1$) was estimated during the times of 4–20 min, and half-life of elimination ($t_{½}$) was calculated from 30 to 180 min. $C_1$ is the extrapolated intercept at zero time of fasting minus the intercept of the slow exponential component; $C_z$ is the extrapolated intercept at zero time of the slow exponential component; $\lambda_1$ ($= \ln 2/t_{½}\lambda_1$) and $\lambda_z$ ($= \ln 2/t_{½}$) are their slopes. The rate constants $k_{21}$, $k_{12}$ and $k_{10}$ were also obtained by this program. The areas under the plasma carnitine concentration–time curves (AUC) were estimated by the linear trapezoidal rule. The plasma clearance ($Cl_P = D_{i.v.}/\text{AUC}$), the central volume of distribution ($V_c = D_{i.v.}/C_1 + C_Z$) and the apparent volume of distribution ($V_z = D_{i.v.}/\lambda_z * \text{AUC}$) were calculated as recommended [17]. Data are reported as means ± standard deviation (SD).

## Results and Discussion

Bolus injections of L-carnitine give no side effects, and no complaints by the patients were noted.

Carnitine is not likely to be metabolized in humans [19] except for partial conversion to acylcarnitine esters. The concentrations of these esters remained essentially unchanged throughout the study and thus pharmacokinetic calculations were performed entirely on the basis of free carnitine values.

The mean plasma concentrations plotted against time after the bolus injections in a linear and a semilogarithmic representation are given in Fig. 1. The concentration of carnitine followed a biexponential course with an initial rapidly declining part (distribution phase) and a terminal log-linear part (elimination phase). In the elimination phase a steady-state equilibrium exists between the central and the peripheral compartment. The calculated pharmacokinetic data are given in Table 1.

An estimation of the carnitine distribution using the biexponential model gave a volume of distribution in the central compartment of 0.12 ± 0.06 l/kg body wt, this being about twice the size of the plasma volume in children [20]. The value is found from the increment of the carnitine concentration observed after 4 min (233.0 ± 78.2 μmol $l^{-1}$) over the basal value (31.4 ± 9.3 μmol $l^{-1}$). This ample increase suggests that the administered carnitine (on average 1 mmol) is in this early phase distributed in about 4 l of the body fluid corresponding to 0.11 l/kg body wt of the patients. After about 30 min the distribution was completed. The apparent volume of distribution, calculated by considering the total value of distribution in the central and peripheral compartments was found to yield 0.27 ± 0.07 l/kg body wt, being approximately that of extracellular space in accordance with the apparent distribution volume of 27% of the body weight found in healthy children [14, 20].

Plasma clearance in uraemic children was markedly decreased (41.2 ± 5.7 ml $min^{-1}$) compared with healthy adults with well functioning kidneys (130 ± 37 ml $min^{-1}$) [13, 14]. In healthy man plasma carnitine values are controlled by tubular reabsorption and consequently the plasma clearance of carnitine is similar to that of endogenous creatinine [14]. In healthy man therefore the main route of L-carnitine elimination is by the kidneys, while tissue influx is presumably low [19]. The considerably impaired renal excretion of carnitine in the face of its fast elimination half-life may suggest however an enhanced influx in tissues. It is known that the uptake of carnitine

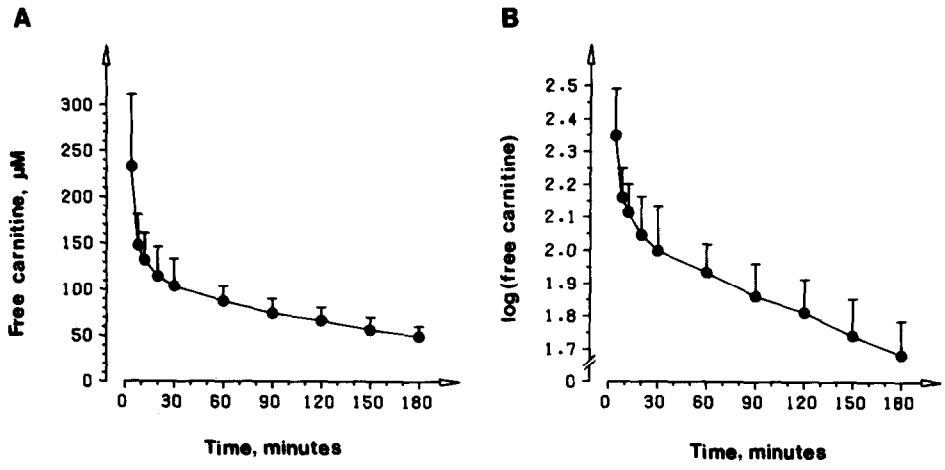


**Figure 1**
Time course of disappearance of L-carnitine (5mg/kg body wt) from plasma after bolus injection in a linear (A) and a logarithmic (B) graph in five haemodialysed children. Results are means ±SD.

**Table 1**
Pharmacokinetic data of intravenous L-carnitine (for abbreviations see methods)

| Patient | 1 | 2 | 3 | 4 | 5 | Means ± SD |
|---|---|---|---|---|---|---|
| Body wt (kg) | 27 | 32 | 37 | 45 | 31 | 34 ± 7 |
| AUC (µmol*h $l^{-1}$) | 302 | 345 | 472 | 502 | 469 | 418 ± 89 |
| $V_c$ (l/kg body wt) | 0.11 | 0.04 | 0.16 | 0.20 | 0.12 | 0.12 ± 0.06 |
| $V_z$ (l/kg body wt) | 0.38 | 0.27 | 0.26 | 0.25 | 0.19 | 0.27 ± 0.07 |
| $CL_P$ (ml $min^{-1}$) | 46.3 | 48.0 | 40.7 | 46.5 | 34.2 | 41.2 ± 5.7 |
| $t_{1/2}$ (h) | 2.53 | 2.11 | 2.72 | 2.78 | 2.00 | 2.43 ± 0.35 |
| $C_z$ (µmol $l^{-1}$) | 78 | 109 | 119 | 124 | 160 | 118 ± 29 |
| $t_{1/2\lambda_1}$ (h) | 0.08 | 0.03 | 0.08 | 0.22 | 0.12 | 0.11 ± 0.07 |
| $C_1$ (µmol $l^{-1}$) | 217 | 691 | 75 | 35 | 109 | 225 ± 270 |
| $k_{21}$ ($h^{-1}$) | 2.53 | 3.05 | 5.28 | 2.48 | 3.45 | 3.36 ± 1.15 |
| $k_{12}$ ($h^{-1}$) | 5.63 | 15.42 | 3.00 | 0.57 | 1.91 | 5.30 ± 5.95 |
| $k_{10}$ ($h^{-1}$) | 0.96 | 2.20 | 0.41 | 0.31 | 0.56 | 0.89 ± 0.77 |

varies considerably in the different tissues as mirrored by the greatly fluctuating $K_M$ and $v_{max}$ values. It is postulated that the maximum uptake rate of carnitine in heart and skeletal muscle is low compared with that in the liver [21], and if this is so the fast elimination as observed in the present study may be due to a rapid liver uptake of carnitine. Nevertheless, in the frame of this investigation the exact destination of the injected carnitine cannot be determined. There are studies in which improvement of lipid metabolism following parenteral carnitine-supplementation is claimed in uraemic patients [9, 22, 23]. Because carnitine is eliminated in healthy man almost entirely by the kidney, there is a theoretical risk of accumulation in patients with renal impairment. The present kinetic evaluation shows no accumulation of carnitine in plasma, but suggests an uptake by carnitine-deficient tissues. It may assist in future evaluations of intravenous carnitine therapy in haemodialysed children.

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