Pharmacokinetic Profiles of Coenzyme Q<sub>10</sub>: Absorption of Three Different Oral Formulations in Rats

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(Received February 19, 2009; Accepted May 21, 2009; Published online June 15, 2009)

Pharmacokinetics and absorption profiles of coenzymeQ<sub>10</sub> (CoQ<sub>10</sub>) from three different oral formulations were evaluated in rats. For the intravenous concentration-time data, a two-compartment open model fitted well. There were no significant changes in the values of the elimination rate constant at the terminal phase, and the half-life of CoQ<sub>10</sub> was estimated to be 7 to 8 hr. The values of intravenous area under the plasma concentration-time curve up to infinity (AUC<sub>∞</sub>) increased with a rise in CoQ<sub>10</sub> dose (0.025 to 2.5 mg/kg); however, the AUC<sub>∞</sub> showed a nonlinear relationship with the administered dose. The total body clearance (CL<sub>tot</sub>) increased with a rise in the intravenous dose of CoQ<sub>10</sub>. The value of CL<sub>tot</sub> increased in proportion to the intravenous dose. Three different formulations of CoQ<sub>10</sub> [olive oil solution (control), sub-nanosize particles and D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS)-emulsion] were tested in rats. An appropriate compartment model wasn’t adapted to the concentration-time data from orally administered CoQ<sub>10</sub> formulations because plasma concentrations of CoQ<sub>10</sub> from 10 to 24 hr after administration were markedly increased for all formulations tested. The TPGS-emulsion showed a significantly higher AUC<sub>0-24</sub> value and absorption rate (Fa) than the other formulations (AUC<sub>0-24</sub>, 18876 ± 6225 ng·h/ml; Fa, 0.15%). There was no difference in the values of AUC<sub>0-24</sub> and Fa between the control and subnano-particle formulations. After intraloop administration of CoQ<sub>10</sub> in the olive oil formulation, there were no significant differences in the plasma concentration of CoQ<sub>10</sub>, and the residual amounts of CoQ<sub>10</sub> in the different parts of the intestinal loop (upper jejunum, lower jejunum, ileum) at the end of experiment were almost the same. These observations indicate that the pharmacokinetics of CoQ<sub>10</sub> are nonlinear, and suggest the existence of a deep compartment for CoQ<sub>10</sub> accumulation in the intestine. Absorption of CoQ<sub>10</sub> from the intestine was very poor; however, a higher plasma concentration of CoQ<sub>10</sub> was achieved by an emulsion formulation using TPGS.

Key words —— coenzymeQ<sub>10</sub>, oral absorption, bioavailability, pharmaceutics, pharmacokinetics

INTRODUCTION

There is growing interest in the use of coenzymeQ<sub>10</sub> (CoQ<sub>10</sub>) as a nutritional supplement. CoQ<sub>10</sub> is a fat-soluble, vitamin-like benzoquinone compound that functions primarily as an antioxidant, a membrane stabilizer, and a cofactor in the oxidative phosphorylation process that leads to the production of adenosine triphosphate (ATP) in its reduced form. CoQ<sub>10</sub> is widely consumed as a food supplement because of its status as an important nutrient for maintaining human health. The rationale for the use of CoQ<sub>10</sub> as a medical agent for treating cardiovascular diseases is based on its fundamental role in mitochondrial function and cellular bioenergetics. With increasing age, the level of CoQ<sub>10</sub> synthesis is reduced, resulting in lower plasma levels of CoQ<sub>10</sub> in elderly people. The absorption of compounds from the gastrointestinal tract is one of the most important determinants of oral bioavailability. Essentially, the oral absorption of highly water-insoluble drugs is frequently limited by poor intestinal-wall permeability. Supplementary CoQ<sub>10</sub> is commonly provided as an oily formulation for oral use; however, the intestinal absorption of supplementary CoQ<sub>10</sub> is slow and limited owing to its hydrophobicity and large molecular weight. Moreover, the absorption of orally administered supplementary CoQ<sub>10</sub> can be
enhanced by interactions with food or food components. There are many reports on investigations of the pharmacokinetic profile of CoQ10 after oral administration. However, the pharmacokinetic results in these reports are inconclusive, and are not accompanied by pharmacokinetic data for intravenous administration of CoQ10.

The objectives of this study were firstly to elucidate the pharmacokinetic properties of CoQ10 intravenously administered at various doses, and secondly to seek formulations that optimize the intestinal absorption of CoQ10 after oral administration.

MATERIALS AND METHODS

Materials —— CoQ10 powder was kindly supplied by Morishita-Jintan Co., Ltd. (Osaka, Japan). D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) was obtained from the Peboc Division of Eastman Chemical Ltd. (Llangefni, U.K.). All other chemicals were of reagent grade, and were used without further purification.

Animals —— Male Wistar rats (300–350 g) were procured from Nippon SLC Co., Ltd. (Hamamatsu, Japan). All animal experiments were performed in accordance with the guidelines for animal experimentation of Doshisha Women’s College of Liberal Arts, Pharmaceutical Division and the Federal Requirements for Animal Studies. The rats had free access to food and water, and were housed in a temperature-controlled facility (22 ± 2°C) with a 12 hr light/dark cycle for at least one week prior to the experiment.

Preparation of Standard and Test Solutions —— The standard stock solutions of CoQ10 were prepared by dissolving in n-hexane at a final concentration of 500 µg/ml, and were then stored at −20°C in the dark. Working standards for a calibration curve were prepared by diluting the standard stock solution with methanol at various concentrations. The calibration curve samples were prepared by adding known amounts of the working standards to plasma or dialysate at a volume ratio of 5:50. The test solutions of CoQ10 for intravenous administration were prepared by dissolving CoQ10 in a vehicle composed of 5% ethanol, 5% Cremophor® EL, and 5% dimethyl sulfoxide in deionized water at a final concentration of 0.025–2.5 mg/kg. The formulations for oral administration were provided by three different types of formula as shown in Table 1. Formulation A is a control prepared by dissolving CoQ10 in olive oil. Formulation B is a water suspension of sub-nano particles (0.4–8.4 µm), which was prepared by a Nanomizer TL-1500 (Tokai Co. Ltd., Tokyo, Japan). Formulation C is an oil-in-water (O/W)-type emulsion using TPGS as an active surfactant, which was prepared by an ultrasonic method. All formulations included 30 mg of CoQ10 per ml.

Intravenous Administration Study —— Rats were fasted for 16–18 hr prior to the experiment, although water was provided ad libitum. Then, the rats were anesthetized by intraperitoneal administration of urethane (1.0 g/kg), and placed in a supine position on a surgical table under an incandescent lamp to maintain body temperature at 37°C. Various test solutions of CoQ10 (0.025–2.5 mg/kg) were administered intravenously to the left jugular vein. Blood samples of 0.12 ml were collected from the right jugular vein at 10, 20, 30 min, 1, 2, 3, 4, and 6 hr after CoQ10 administration. The blank blood samples were taken 5 min prior to the administration of the test solutions. The blood

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Characteristics</th>
<th>Preparation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Control</td>
<td>CoQ10 is dissolved in olive oil</td>
<td>CoQ10 (150 mg) is dissolved in 5 ml of olive oil that is prewarmed at 37°C</td>
</tr>
<tr>
<td>B: Sub-nanosize particle suspension</td>
<td>CoQ10 is crushed to sub-nanosize particles by Nanomizer Mark-II</td>
<td>CoQ10 (1.5 g) is suspended in water including 0.1% Tween 80, and is crushed using the collision power of Nanomizer Mark-II</td>
</tr>
<tr>
<td>C: O/W-type emulsion</td>
<td>A vitamin E derivative, TPGS is used as an emulsifier</td>
<td>To TPGS (1.04 g) dissolved in 8 ml of water, CoQ10 (300 mg), and 2 ml of olive oil are added, and then the mixture is homogenized</td>
</tr>
</tbody>
</table>

Final concentration of CoQ10 in each formulation was set at 30 mg/ml.
samples were collected in heparinized tubes, and plasma was then obtained from whole blood by centrifugation at 12000 × g for 15 min at 4°C, and stored at −80°C until analysis.

**Oral Administration Study** —— Rats were fasted for 16–18 hr prior to the experiment, although water was provided ad libitum. Then, the rats were anesthetized by intraperitoneal administration of urethane (1.0 g/kg), and placed in a supine position on a surgical table under an incandescent lamp to maintain body temperature at 37°C. Rats received CoQ10 formulations orally at doses of 75 mg/kg through a stainless-steel needle. Blood samples of 0.12 ml were collected from the right jugular vein at 0.5, 1, 2, 4, 6, 8, 10, 12, and 24 hr after CoQ10 administration. The blank blood samples were taken 5 min prior to the oral administration of the test formulations. The blood samples were collected in heparinized tubes, and plasma was then obtained from whole blood by centrifugation at 12000 × g for 15 min at 4°C and stored at −80°C until analysis.

**In Situ Intraloop Administration Method** —— Rats were fasted for 16–18 hr prior to the experiment, although water was provided ad libitum. Then, the rats were anesthetized by intraperitoneal administration of urethane (1.0 g/kg), and placed in a supine position on a surgical table under an incandescent lamp to maintain body temperature at 37°C. A midline longitudinal abdominal incision was made, and an inlet or outlet silicon tube (4 mm i.d.) was placed at the upper jejunum, the lower jejunum, and the ileum to make a 15-cm loop. Then, the loop was flushed 3 times with prewarmed (37°C) phosphate buffered saline containing 25 mM glucose (pH 7.4). The test solution of CoQ10 (30 mg/ml in olive oil) was administered to the intestinal loop at a final dose of 75 mg/kg. Blood samples of 0.12 ml were collected from the left jugular vein at 1, 2, 3, 4, 5, and 6 hr after CoQ10 administration. At the end of the experiment, the contents of the intestinal loop were immediately removed, and the amount of CoQ10 remaining in the loop was measured. Plasma was then separated 12000 × g, 15 min, 4°C) and stored at −80°C until analysis.

**Drug Assay** —— CoQ10 in plasma or the intestine was extracted by placing 50 µl of the samples into 1.5 ml polyoxyethylene centrifuge tubes, adding 5 µl of cyclosporine methanol solution (10 µg/ml) as an internal standard, and mixing vigorously for 30 sec. Then, 100 µl of 2% (v/v) ZnSO4 in 50% (v/v) 1-propanol solution was added to precipitate proteins. The mixture was mixed for 10 min, then 0.5 ml of n-hexane was added to extract CoQ10. The mixture was again mixed for 10 min, and then centrifuged at 12000 × g for 3 min. The supernatant was decanted into a glass test tube, and then evaporated until dry in an evaporator for 30 min at 45°C. The residue was reconstituted in 100 µl of methanol-hexane mixture at a ratio of 95:5, and then 20 µl was injected into a liquid chromatography–tandem mass spectrometer (LC-MS-MS) system. The LC-MS-MS analysis was carried out using a high-performance liquid chromatography (HPLC) system consisting of an LC20AD quaternary pump (Shimadzu, Kyoto, Japan) equipped with a vacuum degasser and a SIL 20 A auto sampler with a 100 µl loop (Shimadzu) interfaced with a triple-quadrupole tandem mass spectrometer (Applied Biosystems/MDS Sciex, Burlington, Canada). CoQ10 and cyclosporine were separated on a Cosmosil sorb 5 µm column (2.0 mm in diameter × 50 mm, 5C18-AR-II). The mobile phase, which consists of 100% methanol containing 5 mM ammonium formate acid, was degassed before use. The sample was delivered with a flow rate of 0.4 ml/min at a column temperature of 40°C, with each analysis lasting 8.0 min. The mass spectrometer was operated in the turbo ion spray mode with positive-ion detection. The flow rate of nebulizer gas, curtain gas and collision gas were set at 8, 10, and 6 l/min, respectively, and the ion spray voltage and temperature were set at 5500 V and 400°C, respectively. The declustering potential, the focusing potential, the entrance potential, the collision energy, and the collision cell exit potential were set at 86, 200, 10, 27, and 34 V, respectively. Multiple-reaction monitoring analysis was performed with the transition m/z 880.7 for CoQ10 and m/z 1219.9 for cyclosporine. All raw data were processed with Analyst Software, version 1.4.1. Taking the peak area ratio of CoQ10 against the internal standard, the calibration curves of CoQ10 were made in plasma or intestinal contents without CoQ10. The retention times for CoQ10 and the internal standard were 4.98 and 0.49 min, respectively, and all separation was completed within 8.0 min. The calibration curves of CoQ10 were linear and passed through the origin with correlation coefficients of 0.99 or above. The limit of detection for CoQ10 was 0.005 µg/ml.

**Pharmacokinetic Analysis** —— For intravenous concentration-time data, a two-compartment open model was applied, that is Cₜ = A · e⁻α·t + B · e⁻β·t, where A, B, α, and β represent hybrid model parameters, and the concentration versus time data of
CoQ₁₀ for each rat was fitted to this model using a nonlinear least squares program MULTI, to estimate the value for A, B, α, and β.¹³ Then, the rate constants between central and peripheral compartments (k₁₂, k₂₁ and k₁₀) were calculated. The area under the plasma concentration-time curve up to the final time (t) (AUC₀₋₉) was calculated using a linear trapezoidal rule. The elimination rate constant (λ₂) was estimated analyzing the terminal linear segment of the log serum concentration-time data, followed by extrapolation to infinity (AUC₀₋∞) by adding the value of Cₚ₉/λ₂ to AUC₀₋₉, where Cₚ₉ is the final measurable plasma concentration. The elimination half-life (T₁/₂, λ₂) was calculated from dividing ln2 by λ₂. The volume of distribution at the central compartment (V₁) was calculated as V₁ = D/(A+B), where D represents intravenous dose. The total body clearance (CLtot) was calculated by k₁₀ · V₁, and the volume of distribution at a steady state (Vdss) was calculated by V₁ · (1+k₁₂/k₂₁). The fraction of drug absorbed in vivo (Fa) was determined by the Loo-Riegelman method¹⁴ using free deconvolution software (DE-CONV.xls, D3 Institute, Tokyo, Japan) by calculating on integrating-weight function based on an input one (two-compartment open model for i.v.) and oral data, where the values of α, B, A, and β were utilized.

Statistical Analysis —— Statistical analysis was performed by using the software STATCEL for Windows (OMS Co., Ltd., Tokyo, Japan). All values are expressed as the mean ± standard error of the mean (SEM). Statistical differences of the means were considered significant when p < 0.05 by one-way analysis of variance (ANOVA) followed by Turkey’s multiple range test.

RESULTS

In the intravenous administration study, four different intravenous doses of CoQ₁₀ were tested on rats. Figure 1 shows the plasma concentration-time curves of CoQ₁₀ after intravenous administration. The corresponding pharmacokinetic parameters are listed in Table 2. A two-compartment open model fitted well with the intravenous administration data. There were no significant changes in the values of the elimination rate constant at terminal phase, λ₂. The half-life, T₁/₂, λ₂, was estimated to be 7–8 hr.

<table>
<thead>
<tr>
<th>IV dose</th>
<th>mg/kg</th>
<th>0.025</th>
<th>0.25</th>
<th>1.25</th>
<th>2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_max</td>
<td>h</td>
<td>0.04 ± 0.17</td>
<td>0.38 ± 0.35</td>
<td>0.14 ± 0.10</td>
<td>0.27 ± 0.16</td>
</tr>
<tr>
<td>C_max</td>
<td>ng/ml</td>
<td>484 ± 34</td>
<td>2591 ± 706</td>
<td>3087 ± 699</td>
<td>3983 ± 946</td>
</tr>
<tr>
<td>α</td>
<td>h⁻¹</td>
<td>0.09 ± 0.01</td>
<td>0.11 ± 0.04</td>
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<tr>
<td>V₁</td>
<td>ml/kg</td>
<td>52.3 ± 12.1</td>
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<tr>
<td>Vdss</td>
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<td>84.3 ± 12.3</td>
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<td>506.2 ± 67.3</td>
<td>747.3 ± 106.5</td>
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<tr>
<td>A</td>
<td>ng/ml</td>
<td>245 ± 168</td>
<td>542 ± 429</td>
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<td>1599 ± 997</td>
</tr>
<tr>
<td>β</td>
<td>h⁻¹</td>
<td>1.47 ± 1.32</td>
<td>0.83 ± 0.72</td>
<td>1.68 ± 0.96</td>
<td>1.41 ± 1.06</td>
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</tbody>
</table>

Results of pharmacokinetic analysis of intravenous administration were performed using two-compartment open model described in the text. Each value represents the mean ± S.E. of 4 to 6 rats.

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Analysis of variance was performed by using the software STATCEL for Windows (OMS Co., Ltd., Tokyo, Japan). All values are expressed as the mean ± standard error of the mean (SEM). Statistical differences of the means were considered significant when p < 0.05 by one-way analysis of variance (ANOVA) followed by Turkey’s multiple range test.

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Table 2. Pharmacokinetic Parameters of CoQ₁₀ after Intravenous Administration at Various Doses in Rats

<table>
<thead>
<tr>
<th>IV dose</th>
<th>mg/kg</th>
<th>0.025</th>
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<th>1.25</th>
<th>2.5</th>
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Pharmacokinetic analysis of intravenous administration was performed using a two-compartment open model described in the text. Each value represents the mean ± S.E. of 4 to 6 rats.
The values of AUC∞ increased with a rise in the intravenous dose of CoQ10; however, this relationship was nonlinear. The total body clearance, CLtot, increased with a rise in the intravenous dose of CoQ10, as shown in Fig. 2, this relationship was also nonlinear.

In the oral administration study, three different formulations of CoQ10 were tested on rats. Figure 3 shows the plasma concentration-time curves of CoQ10 after oral administration. The values of AUC0–24 and the corresponding absorption rates, Fa, estimated by the Loo-Riegelman method after oral administration of the three different formulations are listed in Table 3. The CoQ10 in the control formulation completely dissolved in the olive oil, and CoQ10 in the sub-nanosize particle (0.4–8.4 µm; mean particle size, 1.7 ± 0.3 µm) formulation was suspended in water. As shown in Fig. 3, no 1-compartment models fitted to the plasma concentration-time data for the orally administered CoQ10 formulation. Common among the three formulations was the marked increase in plasma concentration of CoQ10 from 10 to 24 hr after administration. The TPGS-emulsion resulted in a much higher AUC0–24 value than the other formulations. The values of AUC0–24 and Fa were 3.7- and 4.7-fold higher, respectively, than those for the control. There was no difference in the values of AUC0–24 and Fa between the control and sub-nanosize particle formulations.

To clarify the absorption site for CoQ10 in the intestine, an in situ loop study was conducted. The intestinal absorption of CoQ10 is shown in Fig. 4. After intraloop administration of the olive oil CoQ10 formulation, there were no significant differences in the plasma concentrations of CoQ10 among the three formulations (Fig. 4a). The residual amounts of CoQ10 in the intestinal loop at the end of the experiment (6 hr after intraloop administration) were almost the same at the three different parts of the intestine (Fig. 4b).

![Fig. 2. Total Body Clearance of CoQ10 Versus Intravenous CoQ10 dose in Rats](image)

The solid line represents a regression line (Y = 8.409e0.886X, R² = 0.991, p < 0.01). Each symbol with bars represents the mean ± S.E. of 4 to 6 rats.

![Fig. 3. Plasma CoQ10 Concentration Versus Time Curves after Oral Administration of Different Three Formulations](image)

The formulations for oral administration are listed in Table 1. All rats received CoQ10 at 75 mg/kg. Key: ●, control; ▲, sub-nanosize particle suspension; ■, TPGS-emulsion. Each symbol with bars represents the mean±S.E. of 6 rats.

<table>
<thead>
<tr>
<th>Formulation*</th>
<th>Control</th>
<th>Sub-nanosize particles</th>
<th>TPGS-emulsion</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0–24</td>
<td>ng·h/ml</td>
<td>6125 ± 2206</td>
<td>5072 ± 1001</td>
</tr>
<tr>
<td>Fa(b)</td>
<td>%</td>
<td>0.0316</td>
<td>0.0341</td>
</tr>
</tbody>
</table>

* Constituents and how to make them are described in the text. b) Fa was calculated by the Loo-Riegelman method using the mean pharmacokinetic data of 0.025 mg/kg intravenous administration. **, p < 0.01 against the control.
Fig. 4. Plasma CoQ10 Versus Time Curves after Intraloop Administration of CoQ10 at Three Different Parts of Intestine
At all intestinal parts, 10-cm-long loop was used. Key: ●, upper jejunum; ▲, lower jejunum; ■, ileum. Each symbol with bars represents the mean ± S.E. of 6 rats.

DISCUSSION

CoQ10 is an essential cofactor in mitochondrial oxidative phosphorylation, and is necessary for ATP production.\(^{15}\) CoQ10 acts as a mobile electron carrier, transferring electrons from NADH CoQ\(_{10}\) reductase or succinate dehydrogenase to the cytochrome b complex.\(^{16}\) The reduced form of CoQ\(_{10}\) is also an antioxidant, and is the only endogenously synthesized lipophilic antioxidant. It can act as an antioxidant directly by protecting biological membranes against oxidants, and can also inhibit the peroxidation of lipoprotein lipids present in the blood.\(^{17}\) Since CoQ10 deficiency in energy metabolism has been shown to be a factor contributing to a number of conditions, many different brands of CoQ10 supplement have been used in the treatment of cardiac, neurologic, oncologic, and immunologic disorders, as well as statin myopathy.\(^{18}\)

However, the bioavailability of CoQ\(_{10}\) is extremely low, and CoQ\(_{10}\) is absorbed from the intestine at a low rate.\(^{19}\) The absorption of orally administered CoQ\(_{10}\) can be enhanced by interactions with food or food components.\(^{4,20}\) In addition, the effect of different formulations of supplements can vary dramatically depending on whether they contain reduced or oxidized CoQ\(_{10}\), whether they are dry powder capsules or CoQ\(_{10}\) dispersed in oil, and whether they contain surfactants and emulsifiers, such as lecithin and polysorbate 80, to improve absorption.\(^{21}\) Moreover, there is also a significant difference in the absorption of CoQ\(_{10}\) from orally administered supplements within and between individuals.\(^{22–24}\)

Although the above points highlight the need for measurement of plasma CoQ\(_{10}\) to monitor the efficacy of different modes of preparation and administration, there is little evidence of the pharmacokinetic benefits of CoQ\(_{10}\) after intravenous or oral administration. Despite the fact that there are several reports containing the results of pharmacokinetic analyses,\(^{14,19,21}\) no clear consensus has been obtained on whether CoQ\(_{10}\) pharmacokinetics can be explained by a certain compartmental model, or on whether the peak plasma concentration of CoQ\(_{10}\) can be predicted. From this perspective, in the first part of the study we examined the pharmacokinetic profiles of CoQ\(_{10}\) after intravenous administration. As shown in Fig. 1, the plasma CoQ\(_{10}\) fitted well with the two-compartment open model, where wellness of curve fitting to the data was judged by a minimum value of Akaike Information criterion.\(^{13}\) The elimination rate constants or half-life at the terminal phase were almost the same for the four dosing groups, indicating that no saturation process in the metabolism or excretion of CoQ\(_{10}\) had occurred. Moreover, CoQ\(_{10}\) is metabolized in all tissues in which metabolites are phosphorylated in the cells, transported in the blood to the kidneys, and then excreted into the urine.\(^{25}\) These observations suggest that CoQ\(_{10}\) consumption in tissue cells occurs in a dose-dependent manner without a saturation process, which is another reason to explain the lack of
change in the elimination profiles after intravenous administration of CoQ_{10}. However, a marked dose-dependent increase in the value of CL_{tot} indicates the possibility that a saturation process of protein binding in the blood exists (Fig. 2, Table 2). We initially investigated the protein binding of CoQ_{10} in rat plasma using an ultrafiltration method, but we were unable to detect it because of a marked adsorption of CoQ_{10} at the membrane filter. However, upon a more detailed analysis, we found that the estimated distribution volume in tissues, V_{dss}, at intravenous doses of 0.025, 0.25, 1.25, and 2.5 mg/kg, were 84.3, 121.4, 506.2, and 747.3 ml/kg, respectively. These observations clearly demonstrate that the tissue distribution of CoQ_{10} at higher intravenous doses above 1.25 mg/kg was markedly increased, suggesting the existence of a saturation process in the protein binding of CoQ_{10} in the blood.

Until now, there were no available pharmacokinetic results to characterize the absorption profiles of orally administered CoQ_{10}. It is well known that the profile of CoQ_{10} absorption from the intestinal tract is markedly and widely affected by the presence of food or by biliary excretion of bile acids.\(^4\) Moreover, several clinical trials and case studies have been conducted to support the use of CoQ_{10} in the prevention and treatment of various conditions and disorders related to oxidative stress.\(^{18}\) However, the large molecular weight (863.63) and lipophilic property of this drug have been shown to limit its oral absorption and consequent efficacy in humans.\(^{26}\) In those reports, similar values of pharmacokinetic parameters such as C_{max}, T_{max}, and/or absorption rate were not determined because of wide variability in the data collected. In our oral administration study over a 24 hr period, the peak plasma levels of CoQ_{10} and the elimination phase were not detected after oral administration of the three formulations tested (Fig. 3). Mean plasma CoQ_{10} concentrations 10 hr after oral administration ranged from 10 to 100 ng/ml, and this concentration range agreed with the results of other pharmacokinetic studies of CoQ_{10}.\(^{4,19,27,28}\) However, in the case of all formulations, the plasma CoQ_{10} concentrations 24 hr after oral administration increased again without providing evidence for an elimination phase. Since the absorption process of CoQ_{10} from the intestinal tract is carried out by micelles,\(^4\) the formation of micelles and the incorporation of poorly water-soluble drugs into micelles are considered to be important factors affecting the absorption.\(^{29}\)

Therefore, regarding the effect of food intake on the plasma concentration of CoQ_{10} after oral administration, it is possible that some food components or bile acids play an important role in the intestinal absorption of CoQ_{10}.

In this study, however, we investigated the absorption profiles of CoQ_{10} from the intestinal tract after oral administration in a fasted condition. Therefore, the effects of micelle formation or food-intake on the absorption profiles were negligible. As shown in Fig. 3, although there were no differences in plasma CoQ_{10} concentrations within 10 hr of oral administration of the three formulations, we found that the plasma concentration from the TPGS-emulsion at 24 hr after administration showed approximately a 7-fold increase, and the AUC_{0-24} of this formulation was 3.7-fold higher than that of the control. The Fa of the TPGS-emulsion, which was estimated using a deconvolution method, was 4.7-fold higher than that of the control (Table 3). These two values are of the same order of magnitude, and suggest that the intestinal absorption of CoQ_{10} from the TPGS-emulsion improves the CoQ_{10} plasma concentration more than the intestinal absorption of CoQ_{10} after oral administration. Wajda et al. reported that CoQ_{10} and vitamin E formulated in Nanosolve\(^\circledR\) (Lipoid GmbH, Ludwigshafen, Germany) improved the bioavailability of CoQ_{10} after oral administration 5-fold.\(^{28}\) In this formulation, CoQ_{10} and vitamin E were emulsified by purified phospholipids obtained by extraction from soybeans, where the phospholipids also act as an emulsifier. TPGS is a water-soluble form of vitamin E modified by polyethylene glycol 1000 succinate.\(^{30}\) TPGS acts as an absorption enhancer to improve the intestinal absorption of cyclosporine, either by decreasing transport back into the intestine by P-glycoprotein (P-gp) or by affecting some unknown mechanism by which cyclosporine is protected from metabolism in the gut.\(^{29}\) In addition, CoQ_{10} interaction affects the transport activity of P-gp, and the efflux transport of CoQ_{10} is mediated by P-gp in Caco-2 cells.\(^{31}\) From these observations, it can be concluded that use of an emulsion formulation with TPGS as an absorption enhancer improves the bioavailability of CoQ_{10} after oral administration more than use of a sub-nanosize particle suspension formulation or an oil-mixed formulation.

To confirm the factors variation in the oral absorption profiles of CoQ_{10}, we tried to determine the intestinal absorption site of CoQ_{10} using an in situ loop study. As shown in Fig. 4, there were no
significant changes in the plasma CoQ_{10} levels after intraloop administration of CoQ_{10} in olive oil. Moreover, the residual amounts of CoQ_{10} in different parts of the loop (upper and lower jejunum, and ileum) 6 hr after administration were almost the same. These findings indicate that there is no specific absorption site for CoQ_{10} in the intestine. Taking the results from Figs. 1, 2, 3, and 4 into consideration, we speculate that there is a deep compartment for CoQ_{10} accumulation in the intestine such as intestinal membranes and lymphatic vessels.

In summary, we have undertaken pharmacokinetic and pharmaceutical study of CoQ_{10}. CoQ_{10} shows nonlinear kinetics, which may be caused by the saturation of protein binding in the blood. In addition, the CoQ_{10} absorption process takes a long time, and we speculate that this may be due to a deep compartment for CoQ_{10} accumulation in the intestine. Absorption of CoQ_{10} from the intestinal tract was very poor; however, a higher plasma concentration of CoQ_{10} was achieved by an emulsion formulation using TPGS.

Acknowledgements This study was supported by Individual Research Grants from Doshisha Women’s College of Liberal Arts (2007). We thank Morishita-Jintan Co., Ltd. (Osaka, Japan) for kindly supplying CoQ_{10}.

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