Pharmacokinetics of Coenzyme Q_{10}

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The pharmacokinetics of coenzyme Q_{10} powder and solution of solubilized form was studied after their oral administration to rats (10 mg/kg). Plasma concentrations of coenzyme Q_{10} were measured by HPLC with electrochemical detection over 48 hours. Solubilized coenzyme Q_{10} exhibited high absorption creating higher plasma concentrations of the drug, as a result of which its bioavailability constituted 264% of that for the powder.

Key Words: *coenzyme Q_{10}; solubilized form; pharmacokinetics; bioavailability*

Coenzyme Q_{10} (ubiquinone) is now recommended as a supplement to traditional therapy for cardiovascular diseases [1,7,9]. Though coenzyme Q_{10} is a lipophilic compound, its solubility is extremely limited and the preparations are often characterized by low bioavailability [8]. Absorption of the substance largely depends on its physicochemical characteristics in the preparation, and hence, coenzyme Q_{10} in powder, suspension, oil solution, or solubilized form exhibits different bioavailability. However, studies of the pharmacokinetic characteristics of coenzyme Q_{10} substance and preparations are extremely rare.

We studied pharmacokinetics of coenzyme Q_{10} powder and solubilized form after single oral administration to rats.

MATERIALS AND METHODS

The study was carried out on male Wistar rats (250-300 g).

The animals were narcotized with pentobarbital (50 mg/kg intraperitoneally) and catheters were implanted under sterile conditions into the femoral arteries for subsequent collection of blood specimens. One day after surgery, conscious animals received coenzyme Q_{10} in a dose of 10 mg/kg (through a tube): solution of solubilized coenzyme Q_{10} (Kudesan, Aquion) in group 1 rats (n=7) and coenzyme Q_{10} powder (suspension in 0.2% methylcellulose gel) in group 2 (n=7).

Blood samples (0.3 ml) were collected before and 2, 3, 4, 5, 7, 9, 24, 32, and 48 h after coenzyme administration. Blood samples were centrifuged, the plasma was collected, frozen, and stored at -20°C until coenzyme Q assay. The animals received no fodder but had free access to water for 2 days after coenzyme Q_{10} administration.

Plasma concentration of coenzyme Q_{10} was measured by a modified previously described method [5]. Ethanol (220 μl) and hexane (550 μl) were added to 100 μl plasma, shaken thoroughly for 10 min, centrifuged at 3000 rpm for 3 min, and the upper layer of n-hexane was collected (500 μl), after which n-hexane was added (550 μl) to the remainder and the extraction procedure and extract collection were repeated. Pooled extract was completely evaporated, dissolved in 100 μl ethanol, and the oxidized forms of coenzymes Q_9 and Q_{10} were reduced by adding 10 μl 5% sodium tetrahydroborate solution in ethanol. Reduced extract (10 μl) was analyzed by HPLC with electrochemical detection on a device manufactured by Environmental Sciences Associate Inc. (model 580 pump and Coulochem II electrochemical detector). The conditions of chromatographic analysis provided separation of coenzymes Q_9 and Q_{10} needed because Q_9 coenzyme was the predominant form of coenzyme Q.

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The separation was carried out in an isocratic mode on a 150×4.6 mm column with C18 adsorbent (5 μ) at the eluent flow rate of 1.3 ml/min. The mobile phase contained 0.3% NaCl in ethanol-methanol-7% $HClO_4$ mixture (970:20:10). Electrochemical detection was carried out using an analytical cell (model 5011) at -50 mV voltage on electrode pair 1 and 350 mV voltage on electrode pair 2. The retention time was 6.5 and 8.5 min for coenzymes Q_9 and Q_{10}, respectively (Fig. 1). Chromatographic data were recorded and processed using Environmental Sciences Associate Inc. software.

The following pharmacokinetic parameters were determined and calculated for coenzyme Q_{10} powder and solubilized form: T_{max} (time needed to attain maximum concentration), C_{max} (maximum concentration), AUC_{o-t} (area under the concentration-time pharmacokinetic curve), C_{max}/AUC_{o-t} (absorption rate). The following parameters were calculated for solubilized form: f (relative bioavailability of the studied dosage form in comparison with the reference form, determined by the $AUC_{o-t,T}/AUC_{o-t,R}$ proportion), f' (relative absorption determined by $C_{max,T}/C_{max,R}$ proportion).

The pharmacokinetic parameters were calculated by the simulation-independent methods. The C_{max} and time needed to attain it were determined by actual concentrations. The area under pharmacokinetic curve (AUC_{o-t}) was calculated by the trapezium method.

Bioavailability of coenzyme Q_{10} was calculated by comparing the areas under plasma coenzyme Q_{10} concentration-time curves, plotted for two groups of rats.

The results are presented as $M\pm m$. The differences between the groups were evaluated using Student's t test and were significant at less than 5% probability of errors ($p<0.05$).

RESULTS

The time needed to attain the maximum plasma concentration of coenzyme Q_{10} (3-4 h) indicates slow absorption of coenzyme Q_{10} in the gastrointestinal tract because of its hydrophobic nature and high molecular weight. The time needed to attain the maximum concentration and absorption rate of coenzyme Q_{10} powder and solubilized form were virtually the same. Other pharmacokinetic parameters of solubilized coenzyme Q_{10} differed significantly from those of the powder form (Fig. 2). The mean plasma concentrations of coenzyme Q_{10} over 24 h after administration of the solubilized form were significantly higher than after powder administration (Table 1). The maximum plasma concentration after the dose of solubilized form was 3.3 times higher and the area under the concentration-time curve was 2.6 times larger than those after powder intake (Table 2). Hence, solubilized coenzyme Q_{10} bioavailability was 264% of the powder form bioavailability and absorption degree 329% of the powder form (Table 2).

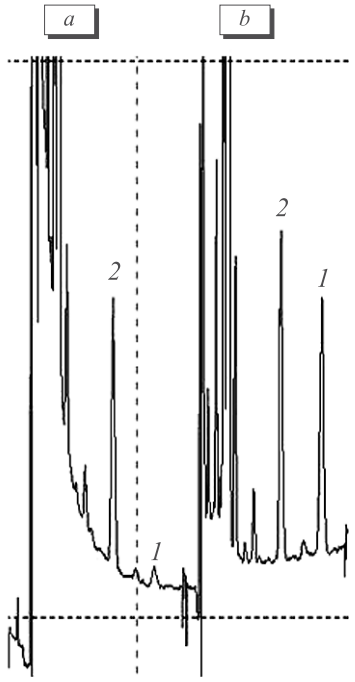

Fig. 1. Chromatograms of two specimens of rat plasma: before (*a*) and 2 h after coenzyme Q_{10} administration (*b*). *1*) coenzyme Q_{10}; *2*) coenzyme Q_9.

TABLE 1. Plasma Concentrations of Coenzyme Q_{10}, Mean for Groups, after Administration of Solubilized and Powder Forms of the Coenzyme (ng/ml; $M\pm m$)

Form	Time after administration, h								
	2	3	4	5	7	9	24	32	48
Solubilized form	414±31	613±82	565±116	368±72	316±58	220±32	175±14	139±21	121±22
Powder	130±22	207±45	212±45	165±23	144±4	123±7	107±14	76±11	71±9
p	<0.00001	<0.001	<0.02	<0.03	<0.02	<0.02	<0.003	<0.02	<0.053

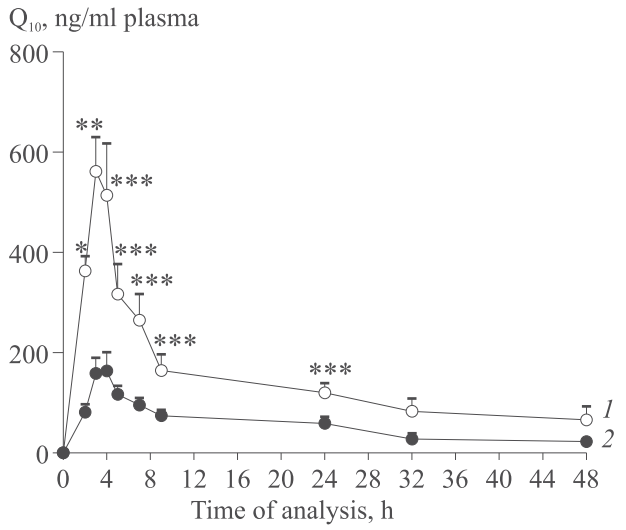

Fig. 2. Kinetic curves of coenzyme Q_{10} concentrations, mean for groups, for solubilized form (*1*) and powder (*2*). **p*<0.00001, ***p*<0.001, ****p*<0.05 compared to *2*.

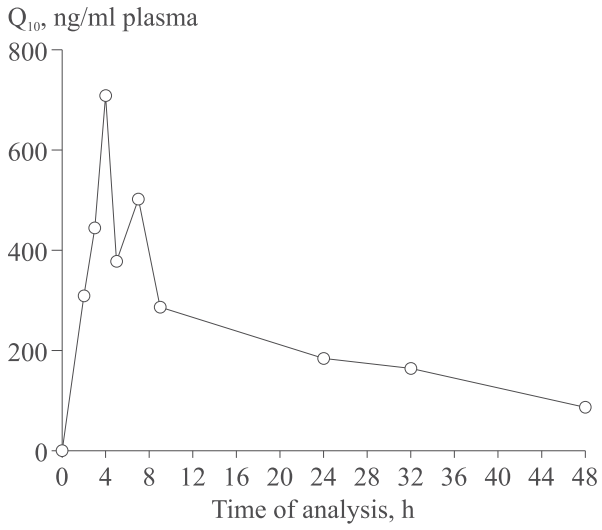

Fig. 3. Individual kinetic curve for coenzyme Q_{10} (solubilized form) with an extra peak.

TABLE 2. Pharmacokinetic Parameters for Coenzyme Q_{10} Solubilized and Powder Forms

Parameter	Solubilized form	Powder	*p*
AUC_{0-48}, ng×h×ml^{-1}	6922±887	2627±350	<0.001
C_{max}, ng/ml	654±52	199±29	<0.00001
T_{max}, h	3.3±0.3	4.3±0.5	Insignificant
C_{max}/AUC_{0-48}	0.103±0.016	0.081±0.015	Insignificant
f, %	264		
f', %	329		

The kinetic curves for coenzyme Q_{10} in some animals had extra peaks observed between hours 7-24 after substance administration (Fig. 3). Oil-soluble coenzyme Q_{10} absorbed in the intestine is captured from the circulation by the liver [3,13]. It seems that the extra peaks of coenzyme Q_{10} concentration observed also in humans [10] and in guinea pig [11] reflect the enterohepatic circulation phenomenon. Episodes of repeated absorption of coenzyme Q_{10} were responsible for "broken" pattern of kinetic curves after the peak concentrations and precluded correct calculation of the elimination constant.

Hence, solubilized coenzyme Q_{10} is obviously preferable due to its better absorption, higher plasma concentrations, and, consequently, better bioavailability. This is in line with published data indicating that plasma concentrations of coenzyme Q_{10} are 2-2.5 times higher during long-term oral therapy with solubilized forms [4] and the bioavailability is 3-6 times higher in comparison with powder [6,12]. The pharmacokinetic advantages of solubilized form are responsible for its high efficiency as a cardioprotector: chronic oral treatment led to an increase of not only plasma levels of coenzyme Q_{10} (2.5 times), but of also its concentration in rat myocardium, which improved survival of cardiomyocytes under conditions of ischemia and eventually limited the size of the postinfarction necrotic zone [2].

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