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Review

Plasma coenzyme Q10 response to oral ingestion of coenzyme Q10 formulations

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Abstract

Plasma coenzyme Q10 (CoQ10) response to oral ingestion of various CoQ10 formulations was examined. Both total plasma CoQ10 and net increase over baseline CoQ10 concentrations show a gradual increase with increasing doses of CoQ10. Plasma CoQ10 concentrations plateau at a dose of 2400 mg using one specific chewable tablet formulation. The efficiency of absorption decreases as the dose increases. About 95% of circulating CoQ10 occurs as ubiquinol, with no appreciable change in the ratio following CoQ10 ingestion. Higher plasma CoQ10 concentrations are necessary to facilitate uptake by peripheral tissues and also the brain. Solubilized formulations of CoQ10 (both ubiquinone and ubiquinol) have superior bioavailability as evidenced by their enhanced plasma CoQ10 responses.

Keywords: Coenzyme Q10; Ubiquinone; Ubiquinol; Plasma coenzyme Q10 concentration; Solubilized coenzyme Q10 formulations; Coenzyme Q10 bioavailability

1. Introduction

Coenzyme Q10 (CoQ10), also known as ubiquinone or ubidecarenone, is a naturally occurring compound with a ubiquitous distribution in nature. Structurally it is similar to vitamin K and its chemical nomenclature is 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone (*trans* configuration). CoQ10 functions like a vitamin in the body, but it is not considered one because unlike vitamins it is synthesized in the body. CoQ10 has a fundamental role in cellular bioenergetics as a cofactor in the mitochondrial electron transport chain and is essential for the production of ATP (Ernster and Dallner, 1995). The functions of CoQ10 in the body go beyond its role in the mitochondria. CoQ10 in its reduced form as the hydroquinone (ubiquinol) is a potent lipophilic antioxidant and thus protects intra- and extra-cellular components from free radical damage. As an antioxidant, CoQ10 is also capable of recycling and regenerating other antioxidants such as tocopherol and ascorbate. In addition, other important functions of CoQ10 such as cell signaling and gene expression have been recognized (Ernster and Dallner, 1995; Crane, 2001; Groneberg et al., 2005).

Numerous health benefits of CoQ10 supplementation have been reported in the literature. A large number of these studies relate to cardiovascular diseases where CoQ10 has been used as an adjunct to standard medical therapy (Greenberg and Frishman, 1990; Overvad et al., 1999; Langsjoen and Langsjoen, 1999; Belardinelli et al., 2006). There is also evidence for its beneficial effect in pediatric cardiomyopathy (Elshershari et al., 2003; Bhagavan and Chopra, 2005). In recent years, CoQ10 is being tested as a therapeutic agent in several neurodegenerative diseases. The importance of CoQ10 in the treatment of mitochondrial diseases is now recognized (DiMauro et al., 2006). Preliminary results with CoQ10 in the treatment of neurologic diseases such as Parkinson's and Huntington's are promising (Kieburtz, 2001; Beal, 2002; Shults et al., 2002; Shults, 2003). The potential therapeutic value of CoQ10 has also become evident in several other conditions (Littarru and Tiano, 2005; Bhagavan and Chopra, 2006).

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Most of the beneficial effects of CoQ10 may be attributed to its fundamental role in mitochondrial energy production.

The purpose of this review is to examine plasma CoQ10 response to orally ingested CoQ10 formulations as an indicator of CoQ10 bioavailability in these products. CoQ10 is available over the counter in various product forms as a dietary supplement in the US and elsewhere, and it has become increasingly popular. CoQ10 is also available as a drug in a few countries. CoQ10 in its pure form is a powder (crystalline) that is insoluble in water and has limited solubility in lipids, and therefore it is poorly absorbed. The importance of product formulation on CoQ10 bioavailability has been suggested previously (Chopra et al., 1998). CoQ10 products currently available on the market include powder-based compressed tablets, chewable tablets, powder-filled hard-shell capsules and softgels containing an oil suspension. The rationale for the latter is that the presence of fat may promote better absorption of CoQ10 since it is lipophilic. In addition, several solubilized formulations of CoQ10 in softgel and liquid forms have become available in recent years. While there is a choice of dosage forms available, one major issue concerning their use whether as a dietary supplement for general well-being or for therapeutic purposes is their potential efficacy. An important determinant of efficacy is absorption/bioavailability of CoQ10 in the various products. Unfortunately, most consumers and also health care professionals are generally unaware of the importance of bioavailability especially as it relates to poorly soluble dietary supplements such as CoQ10. This review deals with data from controlled clinical trials on plasma CoQ10 response to oral ingestion CoQ10 products in order to ascertain which product types have superior bioavailability.

2. Data collection

The data collected in this report are based on controlled clinical trials where plasma CoQ10 data following oral ingestion of various types of CoQ10 formulations are available. The increase in plasma CoQ10 in terms of "fold" increase over baseline and also net increase per 100 mg CoQ10 ingested are taken as indicators of their absorption efficiency. In most of the early clinical trials on CoQ10, plasma CoQ10 determinations were not made. In a few studies where it was done, the analytical procedures employed lacked specificity, sensitivity and precision. Trials carried out beginning in the 1980s have employed HPLC methodology in practically all cases, and studies for this review were selected from this group.

The studies are divided into four distinct categories. The first three deals with chronic low/moderate dose studies, chronic high dose studies, and single dose/pharmacokinetic studies. These studies have all utilized powder-based CoQ10 dosage forms comprised of compressed tablets, chewable tablets, powder-filled capsules, and softgel capsules containing an oil suspension. The fourth category deals with a comparison of the powder-based non-solubilized products with the newer solubilized CoQ10 formulations.

The differentiation of low/moderate and high dose was somewhat arbitrary, with the low/moderate dose range covering a dose of 30 mg to 300 mg a day and the high dose range from 300 mg to 3000 mg a day. One criterion for inclusion in the chronic dosing studies was a minimum of two weeks duration since this assured steady state concentrations of plasma CoQ10 (Tomono et al., 1986; Hosoe et al., 2007). Since there are a large number of studies in the low/moderate range, the selection of the limited number of studies for this evaluation was made randomly. Some of the data shown were extrapolated from figures and these are indicated in the tables. While most of the data in this review relate to studies using CoQ10 as ubiquinone, there are two recent studies that have employed the reduced form of CoQ10 as ubiquinol and these studies are discussed separately.

3. Results

3.1. Studies using CoQ10 as ubiquinone

3.1.1. Chronic low/moderate dose studies

A limited number of studies were randomly selected from a large pool for evaluation of plasma CoQ10 response (Table 1) and they represent typical data in this dose range (30–300 mg for two weeks to nine months). Data for both healthy subjects and patients (mostly CHF) are shown separately in the table. The increase in plasma CoQ10 concentration over baseline in terms of multiples of baseline values (expressed as "fold" increase) was calculated by dividing the final value by the baseline value and this ranged from 1.470 to 4.074. A definite increase with increasing doses of CoQ10 was evident. When the data were calculated in terms of net increase per 100 mg of CoQ10 ingested, there was an overall decreasing trend with increasing dose, with no difference between healthy subjects and patients.

3.1.2. Chronic high dose studies

There were several studies in this group where the dosages of CoQ10 ranged from 300 mg to 3000 mg. Data from three studies using escalating doses of one specific chewable tablet formulations of CoQ10 are shown in Table 2 (Shults et al., 1998, 2002, 2004). As could be expected, the increase in plasma CoQ10 concentration over baseline was much greater with high doses of CoQ10 than that with low/moderate doses of CoQ10. On the other hand, the increase in plasma CoQ10 per 100 mg of CoQ10 ingested was much lower than that with lower doses indicating decreased efficiency of absorption, and this value did not change with increasing dosages in the high dose range.

In one trial using CoQ10 powder as an oil suspension at doses ranging from 300 mg to 900 mg (Ikematsu et al., 2006), the increment in plasma CoQ10 over the baseline

Table 1
Plasma CoQ10 response to chronic ingestion of low/moderate dose CoQ10 in adults using tablets, powder-filled capsules or oil-suspensions

Total daily dose, mg (duration)	*N*	Plasma CoQ10 (μmol/L)		Increase (fold)	Increase per 100 mg	References
		Baseline	Final			
Normal subjects:						
30 (oil susp.) (2 months)	28	1.355	1.992	1.470	2.123	Zita et al. (2003)
50 (powder) (15 days)	20	1.019	1.587	1.557	1.136	Lu et al. (2003)
90 (oil susp.) (2 weeks)	22	0.700[a]	1.950[a]	2.786	1.389	Weber et al. (1994)
90 (oil susp.) (2 months)	20	1.070	2.970	2.776	2.111	Kaikkonen et al. (1997)
90 (powder) (2 months)	20	1.080	2.890	2.676	2.011	Kaikkonen et al. (1997)
100 (oil susp.)[b] (2 weeks)	5	0.656	1.180	1.799	0.524	Lonnrot et al. (1996)
100 (oil susp.) (2 months)	36	1.355	2.930	2.162	1.575	Zita et al. (2003)
200 (oil susp.) (20 days)	15	0.695	2.085	3.000	0.695	Serebruany et al. (1997)
Patients (mostly CHF):						
99 (tablets) (3 months)	27	0.903	2.029	2.247	1.137	Watson et al. (1999)
100 (oil susp.) (3 months)	69	1.170	2.780	2.376	1.610	Hofman-Bang et al. (1995)
100 (oil susp.) (3 months)	17	1.042	2.317	2.224	1.275	Henriksen et al. (1999)
200 (oil susp.) (6 months)	23	1.100	2.548	2.316	0.724	Khatta et al. (2000)
300 (oil susp.) (2 weeks)	62	0.452	1.842	4.074	0.463	Rosenfeldt et al. (2005)
300 (oil susp.) (4 weeks)	23	0.950	3.764	3.962	0.938	Belardinelli et al. (2006)

[a] Extrapolated from figure.
[b] With 500 mg vitamin C.

Table 2
Plasma CoQ10 response to chronic ingestion of high-dose CoQ10 in patients with Parkinson's disease using specific chewable tablet formulations[a]

Total daily dose (mg)	Plasma CoQ10 (μmol/L)		Increase (fold)	Increase per 100 mg
	Baseline	Final		
Shults et al. (1998); $N = 15$; Duration: 1 month (Data extrapolated from figure)				
Placebo	0.680	0.680	1.000	–
400		2.490	3.650	0.450
600		2.900	4.240	0.370
800		3.590	5.260	0.360
Shults et al. (2002); $N = 80$; Duration: 16 months (Data extrapolated from figure)				
Placebo	0.580	0.580	1.000	–
300		1.910	3.310	0.450
600		2.550	4.420	0.330
1200		4.580	7.930	0.330
Shults et al. (2004); $N = 17$; Duration: 2 weeks (Data extrapolated from figure)				
1200	1.160	4.630	4.000	0.290
1800		7.180	6.200	0.340
2400		8.690	7.500	0.310
3000		8.690	7.500	0.250

[a] The chewable CoQ10 tablets used in the above studies contained varying amounts of vitamin E, the total ranging from 800 IU to1500 IU depending on the dose of CoQ10.

showed a slight increase with increasing doses of CoQ10 whereas the increase per 100 mg CoQ10 ingested showed a definite decline with increasing doses of CoQ10 (Table 3). The data are somewhat similar to the results obtained with high dose chewable tablet formulations (Table 2).

3.1.3. Single dose studies

There were several studies in this category and data from four trials covering a dose range of 30 mg to 333 mg are shown in Table 4. The increase per 100 mg values were calculated using the C_{max} data. As in the case of the chronic studies, the increment (fold) in plasma CoQ10 values showed an increase as the dose increased whereas the increase per 100 mg CoQ10 ingested tended to decrease, similar to the findings in the chronic low/moderate dose studies.

3.1.4. Comparison of solubilized vs. powder-based formulations: chronic dose studies

Data from two studies (Chopra et al., 1998) are shown in Table 5. In the first, a solubilized CoQ10 softgel formulation (Q-Gel®) was compared with tablets, powder-filled hard shell capsules and softgels containing an oil suspension. Both the increase (fold) and increase per 100 mg were markedly higher for the solubilized formulation as compared with powder-based non-solubilized formulations.

Table 3
Plasma CoQ10 response to chronic ingestion of high-dose CoQ10 in healthy adults using a softgel formulation containing CoQ10 as an oil suspension

Total daily dose (mg)	Plasma CoQ10 (μmol/L)		Increase (fold)	Increase per 100 mg
	Baseline	Final		
Ikematsu et al. (2006) $N = 88$; Duration: 4 weeks (Data extrapolated from figure)				
300	0.695	3.070	4.420	0.790
600		3.590	5.170	0.480
900		3.710	5.330	0.340

In the second study, only the oil suspension was compared with the solubilized CoQ10 formulation and the results were very similar.

3.1.5. Comparison of solubilized vs. powder-based formulations: single dose studies

A pharmacokinetic evaluation of three solubilized formulations of CoQ10 as compared with a powder-filled hard shell capsule formulation was carried out by Miles et al. (2002). The three solubilized products included a CoQ10 formulation as a syrup (LiQ10®), a softgel formulation (Q-Gel®) and a softgel formulation containing CoQ10 in its reduced form as ubiquinol (Q-Nol®). The three solubilized formulations were found to be far superior to the powder-filled capsules in terms of both increase (fold) and increase per 100 mg, and solubilized ubiquinol was found to be the best of the three solubilized formulations (Table 6).

Molyneux et al. (2004) conducted a single dose study with a number of marketed CoQ10 products using C_{max} (6 h) for comparison (Table 7). Of these, six were non-solubilized formulations (oil suspensions, powder-filled capsules and chewable tablets) and one was a solubilized formulation (Q-Gel®). Again in this study, plasma CoQ10 response was found to be much higher for the solubilized formulation as compared with the non-solubilized formulations.

3.2. Studies using CoQ10 as ubiquinol

3.2.1. Chronic low/moderate dose studies using ubiquinol

Data from a recent study are available where the plasma CoQ10 concentrations were determined following supplementation with 90 mg, 150 mg, and 300 mg of CoQ10 as ubiquinol as an oil suspension for four weeks (Hosoe et al., 2007). This was a dose ranging study, and there was no comparison with any other product. There was a gradual and somewhat linear increase in plasma CoQ10 concentrations with increasing dose. At a daily dose of 300 mg ubiquinol for 4 weeks, plasma ubiquinol concentration reached a markedly high value of 8.413 μmol/L, an 11-fold increase over baseline (Table 8). Likewise, the increase per 100 mg values was also remarkably high compared

Table 4
Plasma CoQ10 response to ingestion of a single low/moderate dose CoQ10 in healthy adults using powder-filled capsules/tablets or oil-suspensions

Dose (mg)	N	Plasma CoQ10 (μmol/L)		Increase (fold)	Increase per 100 mg	References
		Baseline	C_{max}[a]			
30 (oil susp.)	9	1.019	0.359	1.352	1.197	Weber et al. (1997a)
100 (powder)	16		1.163		1.163	Tomono et al. (1986)
100 (oil susp.1)	10		1.330[b]		1.330	Weis et al. (1994)
100 (oil susp.2)	10		0.700[b]		0.700	Weis et al. (1994)
100 (oil susp.3)	10		0.760[b]		0.760	Weis et al. (1994)
100 (powder)	10		0.750[b]		0.750	Weis et al. (1994)
333 (powder)	8	1.645	2.783	2.692	0.808	Lucker et al. (1984)

[a] Corrected for baseline.
[b] Extrapolated from figure.

Table 5
Plasma CoQ10 response to chronic ingestion of low/moderate dose CoQ10 in adults using solubilized and powder-based formulations

Formulation	Plasma CoQ10 (μmol/L)		Increase (fold)	Increase per 100 mg
	Baseline	Final		
Chopra et al. (1998); Study 1: $N = 24$; Dose: 120 mg; Duration: 3 weeks				
Solubilized (softgel caps)[a]	0.579	3.824	6.622	2.713
Oil-suspension	0.579	1.587	2.740	0.840
Tablets	0.602	1.853	3.078	1.043
Powder-filled caps	0.579	1.888	3.261	1.091
Chopra et al. (1998): Study 2: $N = 24$; Dose:120 mg; Duration: 4 weeks				
Solubilized (softgel caps)[a]	0.440	3.243	7.370	2.336
Oil-suspension	0.463	1.459	3.151	0.830

[a] Q-Gel®.

Table 6
Plasma CoQ10 response to ingestion of a single low/moderate dose CoQ10 in adults using solubilized and powder-based formulations

Formulation	Plasma CoQ10 (μmol/L)		Increase (fold)	Increase per 100 mg
	Baseline	C_{max}		
Miles et al. (2002); $N = 9$ (crossover); Dose: 180 mg (2.1 mg/kg)				
Solubilized (syrup)[a]	0.602	1.795	2.982	0.663
Solubilized (softgel caps)[b]	0.602	1.795	2.982	0.663
Solubilized (ubiquinol caps)[c]	0.602	2.073	3.444	0.817
Powder (caps)	0.602	0.741	1.231	0.077

[a] LiQ10®.
[b] Q-Gel®.
[c] Q-Nol®.

Table 7
Plasma CoQ10 response to ingestion of a single low/moderate dose CoQ10 in adults using solubilized and powder-based formulations

Formulation	Plasma CoQ10 (μmol/L)		Increase (fold)	Increase per 100 mg
	Baseline	C_{max}		
Molyneux et al. (2004); $N = 10$ (cross-over); Dose: 150 mg				
Solubilized[a]	0.850	1.436	1.689	0.391
Suspension 1 (softgel caps)	0.850	1.171	1.378	0.214
Suspension 2 (softgel caps)	0.850	1.079	1.269	0.153
Suspension 3 (softgel caps)	0.850	1.027	1.208	0.118
Suspension 4 (softgel caps)	0.850	1.023	1.204	0.115
Powder-filled caps	0.850	1.053	1.239	0.135
Chewable tablets	0.850	0.989	1.164	0.093

[a] Q-Gel®.

with results obtained with both high and low/moderate dose powder-based CoQ10 formulations in the form of ubiquinone.

3.2.2. Chronic low and high dose studies using ubiquinol

In a recent trial, a unique solubilized formulation of CoQ10 in its reduced form as ubiquinol (Li-Q-Nol®) was tested in children at both low and high doses, viz. 1 mg/kg/d and 10 mg/kg/d each for one month duration (Miles et al., 2006). Plasma CoQ10 values, extrapolated to a dosage of 600 mg a day for an adult, 60 kg, for purposes of comparison with adult dosages, are shown in Table 9. The plasma response at this dosage was comparable to data from studies involving much higher doses of CoQ10 as ubiquinone (2400 mg–3000 mg a day). The increase in per 100 mg CoQ10 ingested was also much higher at the 600 mg dose with solubilized ubiquinol as compared with other high dose studies using much higher doses of powder-based CoQ10 formulations as ubiquinone (Tables 2 and 3).

3.2.3. Single dose studies using ubiquinol

In one study referred to earlier (Miles et al., 2002), a solubilized formulation of ubiquinol was compared with a powder-filled capsule and two solubilized formulations of CoQ10 based on ubiquinone with respect to their pharmacokinetic parameters (Table 6). While the three solubilized formulations were far superior to the powder-based product, solubilized ubiquinol was found to be even better than the two solubilized ubiquinone-based products.

In a very recent study, ubiquinol as an oil suspension was tested at two doses, viz. 150 mg and 300 mg (Hosoe et al., 2007). The C_{max} values (6 h) were 2.173 μmol/L and 3.686 μmol/L, and the increases over plasma baseline concentrations were 2.3-fold and 4.7-fold, respectively (Table 10). Both the net increase in plasma ubiquinol concentration and the increase per 100 mg were higher as com-

Table 8
Plasma CoQ10 response to chronic ingestion of low/moderate dose CoQ10 as ubiquinol[a] in adults

Total daily dose (mg)	Plasma CoQ10 (μmol/L)		Increase (fold)	Increase per 100 mg
	Baseline	Final		
Hosoe et al. (2007); Duration: 4 weeks				
90 (20)[b]	0.659	3.282	4.981	2.926
150 (20)	0.751	4.437	5.908	2.457
300 (19)	0.763	8.413	11.026	2.550

[a] Softgel formulation containing emulsified CoQ10 as ubiquinol (Kaneka QH™).
[b] Figures in parentheses indicate the number of subjects.

Table 9
Plasma CoQ10 response to chronic ingestion of high-dose CoQ10 in children using a liquid formulation containing solubilized CoQ10 as ubiquinol (Li-Q-Nol®)[a]

Total daily dose (mg/kg/d)	Plasma CoQ10 (μmol/L)		Increase (fold)	Increase per 100 mg[b]
	Baseline	Final		
Miles et al. (2006); $N = 16$; Duration: 1 month (Data extrapolated from figure)				
1 (run-in)	0.950	3.000	3.158	3.416
10 (od)		8.500	8.947	1.258
10 (bid)		10.700	11.263	1.625

[a] A solubilized ubiquinol formulation as a syrup.
[b] Extrapolated to an adult weighing 60 kg; Equivalent adult dose of 60 mg and 600 mg, respectively.

Table 10
Plasma CoQ10 response to ingestion of a single low/moderate dose CoQ10 as ubiquinol[a] in adults

Formulation (mg)	Plasma CoQ10 (μmol/L)		Increase (fold)	Increase per 100 mg
	Baseline	C_{max}		
Hosoe et al. (2007); $N = 15$				
150	0.945	2.173	2.300	0.819
300	0.784	3.686	4.702	0.964

[a] Softgel formulation containing emulsified CoQ10 (Kaneka QH™).

pared with single dose studies using non-solubilized CoQ10 formulations in the form of ubiquinone at similar dosages.

4. Discussion

4.1. Studies using CoQ10 as ubiquinone

4.1.1. Chronic low/moderate dose studies

The data on plasma responses to low/moderate doses were derived mostly from studies employing CoQ10 as an oil suspension in softgel capsules since these are more commonly available products (Table 1). Overall, there was a gradual increase in plasma CoQ10 values expressed in terms of ''fold' increase over baseline CoQ10 concentrations whereas the increase per 100 mg CoQ10 ingested showed a decreasing trend with increasing dosage. This shows that in the low/moderate dose group ranging from 30 mg to 300 mg, the efficiency absorption decreases as the dose increases.

4.1.2. Chronic high dose studies

The data on high dose studies reported in Table 2 were based entirely on the use of one specific powder-based chewable tablet formulation of CoQ10. As could be expected, plasma CoQ10 concentrations and the increment over baseline values showed a gradual increase with increasing dosage of CoQ10 (Tables 2 and 3; data extrapolated from figures), and this response was much greater than that seen with low/moderate doses (Table 1). An examination of the data covering the entire dose range, from 30 mg to 3000 mg, shows that the plasma concentrations tend to plateau at around 2400 mg with no further increase at 3000 mg, using one specific chewable tablet formulation of CoQ10 (Shults et al., 2004). This was confirmed in a subsequent study using the same chewable tablet formulation of CoQ10 (Ferrante et al., 2005).

There was a striking reduction in the net increase in plasma CoQ10 concentration per 100 mg CoQ10 ingested in the high dose studies as compared with the data from low/moderate dose studies. This shows that the efficiency of absorption decreases sharply in the high dose range, and this would be as expected for a fat soluble nutrient such as CoQ10 ingested at pharmacologic doses.

In all the three high dose studies shown in Table 2, the specific CoQ10 chewable tablet formulations used contained rather large amounts of vitamin E contributing to total daily intake ranging from 800 IU to 1500 IU depending upon the dose of CoQ10. Since it is known that high dose vitamin E ingested along with CoQ10 may interfere with CoQ10 absorption and thus result in lower plasma CoQ10 concentrations (Chopra and Bhagavan, 1999; Kaikkonen et al., 2000), the figures on the increase in plasma CoQ10 concentration and in net increase per 100 mg shown in the table may be somewhat underestimated for similar CoQ10 dosage forms of the same strength that do not contain vitamin E.

4.1.3. Single dose studies

The four studies shown in Table 4 are single dose pharmacokinetic studies using low to moderate doses of CoQ10. The overall response pattern to CoQ10 ingestion is quite similar to that seen in the chronic dose studies, i.e., with an increasing dose of CoQ10, an increase in C_{max} and a decrease in net increase per 100 mg. The T_{max} in these studies is consistently around 6 h which shows that CoQ10, a rather large molecule which is water-insoluble, is absorbed slowly in the intestine.

4.1.4. Comparison of solubilized vs. powder-based CoQ10 formulations: chronic dose studies

Bioavailability assessments of a solubilized CoQ10 formulation (Q-Gel®) introduced in the mid 1990s were carried out by Chopra et al. (1998). There were two studies and in the first, it was compared with three non-solubilized formulations (tablets, powder-filled capsules and an oil suspension), and with an oil suspension only in the second study. The results from both the studies clearly showed the enhanced bioavailability of the solubilized CoQ10 formulation.

4.1.5. Comparison of solubilized vs. powder-based CoQ10 formulations: single dose studies

In one study by Miles et al. (2002), the pharmacokinetic profiles of three solubilized CoQ10 formulations were compared with that of a powder-based formulation following a single dose. The solubilized products also included a novel reduced form of CoQ10 as ubiquinol in a softgel

formulation (Q-Nol®). The three solubilized formulations were found to be far superior to the powder-filled capsules in terms of both increase (fold) and net increase per 100 mg ingested, and the solubilized ubiquinol was found to be the best of the three solubilized CoQ10 formulations.

Molyneux et al. (2004) conducted a single dose study with a number of marketed CoQ10 products using a rather simple design. They employed C_{max} (6 h) for comparison of plasma CoQ10 responses as an indicator of bioavailability of the various products. Of the seven products tested, six were powder-based formulations (oil suspensions, powder-filled capsules and chewable tablets) and one was a solubilized formulation (Q-Gel®). The increase in plasma CoQ10 was much higher with the solubilized formulation than that with the powder-based formulations, and this is consistent with previous findings on the superiority of solubilized CoQ10 formulations (Chopra et al., 1998; Miles et al., 2002; Zaghloul et al., 2002).

4.2. Studies using CoQ10 as ubiquinol

4.2.1. Chronic low/moderate dose studies

In a dose-ranging study, Hosoe et al. (2007) administered daily doses of 90 mg, 150 mg, and 300 mg ubiquinol (as an oil suspension in softgel capsules, Kaneka QH™) to healthy adults for four weeks and found remarkably high plasma CoQ10 concentrations (as ubiquinol), up to 11-fold increase over baseline at the 300 mg dose. In their study, plasma ubiquinol accounted for 96%–98.5% of plasma CoQ10 at all the four data points. In terms of increase over baseline (fold) and net increase per 100 mg CoQ10 ingested, these numbers are impressive indicating superior absorption of CoQ10 in the form of ubiquinol (Table 8). The fact that there was only a slight difference between the 90 mg, 150 mg, and 300 mg doses with respect to increase per 100 mg (2.926, 2.457, and 2.550, respectively) indicates that the efficiency of absorption was not appreciably affected with increasing doses of ubiquinol in this dose range. It would be of interest to examine at what point does this begin to show a decrease as the dose increases beyond 300 mg. It may be noted that the data for the 150 mg dose are comparable to those of Chopra et al. (1998) for solubilized CoQ10 formulation as ubiquinone at a dose of 120 mg (Table 5).

4.2.2. Chronic high dose studies

Miles et al. (2006) employed a novel liquid formulation of CoQ10 as ubiquinol in the form of syrup (Li-Q-Nol®) in a dose-ranging study with children (Table 9). While the results were somewhat similar to those with adults in terms of plasma CoQ10 concentrations (Table 2), the plasma CoQ10 response was far greater when compared on the basis of dosage. The comparison was based on an equivalent adult dosage of 600 mg for an individual weighing 60 kg. Furthermore, when the dosage was administered in two divided doses, the response was even higher. This is not surprising and it shows that split-dosing is more effective especially when administering pharmacologic doses of CoQ10. A similar effect has been observed with CoQ10 administered as ubiquinone (Singh et al., 2005).

The highest net increase in plasma CoQ10 concentration and also the highest increase per 100 mg CoQ10 ingested was observed using solubilized CoQ10 as ubiquinol at a dose of 600 mg (Miles et al., 2006), and these values are higher than those obtained with much larger doses of CoQ10 (up to 3000 mg) as ubiquinone. According to the authors, after correcting for body weight differences, the dosage of CoQ10 (as ubiquinol) employed in their study was approximately 3-fold lower than that reported by Shults et al. (2004) using a specific chewable CoQ10 tablet formulation at a daily dose of 2400 mg.

Incidentally, the highest plasma CoQ10 concentration reported in the literature thus far is 10.7 μmol/L that was achieved using CoQ10 in the form of ubiquinol (Miles et al., 2006). Whether this represents a value close to a ceiling for plasma CoQ10 needs to be established. Furthermore, it would be important to determine whether such high plasma concentrations afford maximum therapeutic benefit.

4.2.3. Single dose studies

In the pharmacokinetic study by Miles et al. (2002), solubilized ubiquinol in a softgel formulation was one of the products tested along with two solubilized CoQ10 formulations as ubiquinone and a powder-filled capsule (Table 6). While the solubilized CoQ10 formulations were found to be far superior to the powder-based product, solubilized ubiquinol was found to be the best of the three solubilized formulations in terms of pharmacokinetic profile, increase over baseline (fold) and net increase per 100 mg CoQ10 ingested.

The single dose study by Hosoe et al. (2007) employed ubiquinol as an oil suspension (Kaneka QH™) at two doses, viz. 150 mg and 300 mg (Table 10). The plasma CoQ10 (ubiquinol) response at C_{max} (6 h) was higher than that in studies using CoQ10 as ubiquinone (Tables 4 and 6). The data for the 150 mg dose is comparable to the ubiquinol data of Miles et al. (2002) at a dose of 180 mg (Table 6).

Both the chronic dose and single dose studies clearly demonstrate that solubilized formulations of CoQ10 whether in the form of ubiquinone or as ubiquinol are superior to non-solubilized CoQ10 formulations in terms of plasma CoQ10 response. This reflects the superior bioavailability of solubilized CoQ10 formulations, and solubilized ubiquinol appears to be even better than solubilized ubiquinone. With non-solubilized formulations of CoQ10, data show that ubiquinol is superior to ubiquinone.

4.3. Pharmacokinetic profile of CoQ10

4.3.1. Ubiquinone

There are several studies that provide data on the pharmacokinetic parameters of orally ingested CoQ10 in the

form of ubiquinone. The paper by Tomono et al. (1986) that is cited often has provided useful basic information on the pharmacokinetic parameters of ubiquinone. A T_{max} of about 6 h for ubiquinone has been confirmed by others (Weis et al., 1994; Weber et al., 1997a; Miles et al., 2002). This shows that CoQ10 is slowly absorbed in the GI tract and this is attributable to its hydrophobicity and relatively large molecular weight. The T_{max} is apparently not affected in the case of sustained release tablets (Lu et al., 2003). The steady-state T_{max} appears to be somewhat lower at about 5 h (Lucker et al., 1984). A second plasma CoQ10 peak has been observed at about 24 h following oral ingestion of ubiquinone (Lucker et al., 1984; Tomono et al., 1986; Weis et al., 1994) which could be attributed to both enterohepatic recycling and redistribution from the liver to circulation primarily via the LDL/VLDL fractions.

4.3.2. Ubiquinol

Solubilized and stabilized formulations of ubiquinol became available a few years ago. Miles et al. (2002) conducted the first pharmacokinetic study with ubiquinol using a softgel formulation along with three other products based on ubiquinone. The pharmacokinetic profile of ubiquinol was identical to that of ubiquinone with a T_{max} at 6 h except that the plasma response of ubiquinol was much greater. There was also a shoulder at 24 h that is indicative of a second peak. Hosoe et al. (2007) have confirmed these findings on ubiquinol and furthermore, their data is suggestive of an additional shoulder peak at 12 h. Although the elimination half-life of ubiquinol could not be accurately determined in their study, it was estimated to be about 48 h.

That the pharmacokinetic profiles of ubiquinone and ubiquinol are identical is not surprising due to the fact that circulating CoQ10 is almost entirely in the form of ubiquinol (Yamashita and Yamamoto, 1997; Tang et al., 2001; Miles et al., 2003) and that the conversion of ubiquinone to ubiquinol occurs in the enterocytes prior to its lymphatic transport into circulation (Mohr et al., 1999; Craft et al., 2005; Bhagavan et al., 2007).

4.4. Other factors influencing plasma CoQ10 concentrations

Apart from the expected increase in plasma CoQ10 concentrations following oral ingestion of CoQ10 formulations, there are other factors that have an influence on plasma CoQ10 values. Dietary fat is known to improve CoQ10 absorption. Dietary contribution of CoQ10 is minimal unless one is consuming rather large quantities of organ meats such as cooked pork heart (Weber et al., 1997a). The intake of CoQ10 from a typical Western diet has been estimated to be about 3–5 mg a day, primarily derived from meat and poultry (Weber et al., 1997b). There is evidence to show that high dose vitamin E ingested along with CoQ10 may interfere with CoQ10 absorption and thus result in lower plasma CoQ10 (Chopra and Bhagavan, 1999; Kaikkonen et al., 2000), This may be due to competition during the absorption process in the intestine. Other determinants of plasma CoQ10 include serum cholesterol, serum triglycerides, gender, alcohol consumption, and age (Kaikkonen et al., 1999, 2002).

There is evidence to show that exogenously administered CoQ10 does not down-regulate endogenous synthesis of CoQ10. This is borne out by the fact that plasma CoQ10 concentrations return to their baseline values but not lower after cessation of CoQ10 supplementation regardless of the dose whether as ubiquinone (Tomono et al., 1986; Ikematsu et al., 2006) or as ubiquinol (Hosoe et al., 2007). This finding is consistent with previous data from animal studies (Zhang et al., 1995).

4.5. Plasma CoQ10 measurements in clinical trials

The importance of monitoring plasma CoQ10 concentrations in clinical trials involving pharmacologic doses of CoQ10 cannot be overemphasized (Bhagavan et al., 2001; Steele et al., 2004). Higher than "normal" plasma CoQ10 concentrations appear to be necessary to promote uptake by peripheral tissues and also to cross the blood brain barrier. The plasma threshold for the uptake of CoQ10 appears to be different for different tissues. For instance, in one study with congestive heart failure patients, it was reported that those with a plasma CoQ10 value of 2.4 μg/mL (2.780 μmol/L) showed the highest benefit (Belardinelli et al., 2006). In an earlier study with CHF patients, it was reported that a blood CoQ10 concentration of at least 3.5 μg/mL (4.054 μmol/L) appeared to be necessary before any therapeutic benefit from CoQ10 supplementation could be expected (Langsjoen and Langsjoen, 1998). The plasma threshold appears to be much higher for neurodegenerative diseases such as Huntington's (Kieburtz, 2001) and Parkinson's (Shults et al., 2002), based upon the CoQ10 dosages required to achieve clinical response and also on blood CoQ10 data where available (Shults et al., 2002).

In this context, it may be noted that there are a few studies often cited in the literature where the beneficial effects of CoQ10 supplementation in heart disease could not be demonstrated (Watson et al., 1999; Khatta et al., 2000; Permanetter et al., 1992). Plasma CoQ10 data following CoQ10 supplementation are available only for the first two studies (2.029 μmol/L for Watson et al. and 2.548 μmol/L for Khatta et al.) and both are below the indicated threshold for heart disease patients. It therefore appears that this could have been at least one factor contributing to the lack of beneficial effect of CoQ10 in these studies, which could be attributed to both the dosage and also the bioavailability of the products used.

4.6. Redox status of plasma CoQ10

Plasma CoQ10 is present almost entirely (about 95%) in its reduced form as ubiquinol in healthy subjects (Yamashita and Yamamoto, 1997; Tang et al., 2001; Miles

et al., 2003). The redox status is not affected by gender or race (Miles et al., 2003). Furthermore, orally ingested CoQ10, whether as ubiquinone or as ubiquinol and regardless of the dose, appears in circulation as ubiquinol with no change or very little change in its redox status (Kaikkonen et al., 2000; Mohr et al., 1992; Weber et al., 1994; Hosoe et al., 2007). This shows that there is an efficient mechanism to convert orally administered CoQ10 as ubiquinone to ubiquinol in vivo. There is evidence to show that this reduction takes place in the intestine following absorption before CoQ10 enters the lymphatic system. This was demonstrated in a recent study using Caco-2 cells in culture that the reduction occurs in the enterocytes (Craft et al., 2005; Bhagavan et al., 2007). It was shown in an earlier experiment with rats that orally administered CoQ9 (major homolog in rats) and also CoQ10 were recovered as the corresponding ubiquinols in mesenteric lymph, thus demonstrating their reduction to corresponding ubiquinols in the intestine (Mohr et al., 1999). It is of interest to note in this context that the redox status of CoQ10 in plasma may serve as a sensitive biomarker for oxidative stress (Yamashita and Yamamoto, 1997; Miles et al., 2005).

5. Summary

Plasma CoQ10 concentrations and also the net increase over baseline plasma CoQ10 values show a gradual increase with increasing dose of CoQ10 from low/moderate to high doses. Not surprisingly, the efficiency of absorption decreases as the dose increases, and this is particularly striking at high doses. Split dosing is superior to single dosing with pharmacologic doses of CoQ10. Plasma CoQ10 concentrations appear to plateau at 2400 mg using one specific chewable tablet formulation of CoQ10.

Highest plasma CoQ10 concentration reported thus far is 10.7 μmol/L using a solubilized ubiquinol formulation. Whether this value is close to a ceiling for plasma CoQ10 is not known at this time. Furthermore, whether such high plasma concentrations maximize the therapeutic potential of CoQ10 needs to be explored.

About 95% of circulating CoQ10 is present in its reduced form as ubiquinol in healthy subjects and this ratio is not affected by oral ingestion of CoQ10 either as ubiquinone or as ubiquinol. Plasma redox status of CoQ10 appears to be a sensitive biomarker for oxidative stress.

Plasma CoQ10 concentrations need to be high (i.e. higher than ''normal'' values) in order to promote uptake by peripheral tissues and possibly also to cross the blood brain barrier. The plasma threshold for uptake appears to be different for different tissues. Among non-solubilized formulations of CoQ10, ubiquinol has been found to be superior to ubiquinone in its plasma CoQ10 response. The response following ingestion of solubilized formulations of CoQ10 is much greater indicating their superior bioavailability as compared with non-solubilized powder-based CoQ10 products (compressed tablets, chewable tablets, powder-filled capsules, and softgels containing a suspension in oil). Solubilized formulations of ubiquinol appear to be even better than solubilized ubiquinone. Thus, comparably high or even higher plasma CoQ10 concentrations may be achieved using much lower doses of the solubilized CoQ10 formulations, and this is of particular importance in neurodegenerative diseases where higher plasma concentrations appear to be necessary for therapeutic benefit. The beneficial effects of CoQ10 may be largely attributed to its fundamental role in mitochondrial function and cellular bioenergetics.

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