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Study on safety and bioavailability of ubiquinol (Kaneka QH™) after single and 4-week multiple oral administration to healthy volunteers

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Abstract

The safety and bioavailability of ubiquinol (the reduced form of coenzyme Q_{10}), a naturally occurring lipid-soluble nutrient, were evaluated for the first time in single-blind, placebo-controlled studies with healthy subjects after administration of a single oral dose of 150 or 300 mg and after oral administration of 90, 150, or 300 mg for 4 weeks. No clinically relevant changes in results of standard laboratory tests, physical examination, vital signs, or ECG induced by ubiquinol were observed in any dosage groups. The C_{max} and $AUC_{0-48\,h}$ derived from the mean plasma ubiquinol concentration-time curves increased non-linearly with dose from 1.88 to 3.19 μg/ml and from 74.61 to 91.76 μg h/ml, respectively, after single administration. Trough concentrations had nearly plateaued at levels of 2.61 μg/ml for 90 mg, 3.66 μg/ml for 150 mg, and 6.53 μg/ml for 300 mg at day 14, and increased non-linearly with dose in the 4-week study. In conclusion, following single or multiple-doses of ubiquinol in healthy volunteers, significant absorption of ubiquinol from the gastrointestinal tract was observed, and no safety concerns were noted on standard laboratory tests for safety or on assessment of adverse events for doses of up to 300 mg for up to 2 weeks after treatment completion.

Keywords: Ubiquinol; Ubiquinone; Coenzyme Q_{10}; Safety; Bioavailability; Healthy volunteer

1. Introduction

Coenzyme Q_{10}, which is also known as ubiquinone, is a lipid-soluble, vitamin-like substance present in nearly all human tissues and involved in essential cellular processes of energy production in mitochondria, where it acts as both an electron carrier and proton translocator during cellular respiration and ATP production (Arroyo et al., 2000; Nohl et al., 2001; Crane, 2001; Kagan et al., 2001; Villalba et al., 2001). In its reduced form (ubiquinol), coenzyme Q_{10} acts as an antioxidant in both mitochondria and lipid membranes by either scavenging free radicals directly or in conjunction with α-tocopherol (Quinn et al., 1999; Lass and Sohal, 2000; Forsmark-Andree et al., 1997; Noack et al., 1994). Because of its important biological roles, coenzyme Q_{10} has been widely used as a dietary supplement by health-conscious individuals and those with ailments including various cardiac disorders (Overvad et al., 1999; Greenberg and Frishman, 1990; Hendler and Rorvik, 2001; Tran et al., 2001; Jones et al., 2002).

Ubiquinol is the most common form of coenzyme Q_{10} in vivo, and accounts for more than 80% of the total ubiquinol + ubiquinone pool in human plasma, intestine, and liver (Okamoto et al., 1989; Frei et al., 1990; Åberg et al., 1992). In addition, Mohr et al. (1992), Stocker and Suarna (1993), Weber et al. (1994) reported that following dietary supplementation with coenzyme Q_{10}, efficient reduction of coenzyme Q_{10} to ubiquinol occurs either during absorption or rapidly after the appearance of coenzyme

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Q_{10} in the blood. We recently measured the ubiquinol contents of various foods (9 types of meat, 13 types of fish/shellfish, 12 vegetables, and chicken egg) using high performance liquid chromatography (HPLC) with an electrochemical detector. Ubiquinol was identified in most of the foods analyzed, and the mean percentages of ubiquinol in total coenzyme Q_{10} [ubiquinol contents × 100/(ubiquinol + ubiquinone contents)] were 33.5%, 25.8%, 17.2%, and 34.6% in meats, fishes/shellfishes, vegetables, and chicken egg, respectively (Fujii et al., 2006). Cabrini et al. (2001) reported that the percentages of ubiquinol in total coenzyme Q_{10} in extra virgin olive oil, peanut oil, soybean oil, corn oil and sunflower oil were 10.5%, 87.5%, 73.5%, 75.0% and 90.3%, respectively. Furthermore, we found that when rats were orally administered a single-dose (100 mg/kg) of ubiquinol or ubiquinone dissolved in olive oil, there was an approximately 2-fold difference in area under the plasma total coenzyme Q_{10} concentration curve between the two agents, indicating that ubiquinol has higher bioavailability than ubiquinone (Mae et al., 2001).

Occurrence of ubiquinol in human body and foods, the good bioavailability of ubiquinol, and the fact that ubiquinol is a potent lipophilic antioxidant and that it is the most common form of coenzyme Q_{10} in vivo suggested the possibility of use of ubiquinol as a new novel dietary supplement. However, development of it as a dietary supplement was difficult because it is readily oxidized in air. Recently, however, our chemical research group established a method enabling manufacture of ubiquinol bulk as Kaneka QH™ from our ubiquinone bulk of Kaneka Q10™, as well as stable capsule product containing Kaneka QH™.

In order to assess the safety of Kaneka QH™ (ubiquinol), a series of preclinical safety studies were performed in compliance with relevant Good Laboratory Practice (GLP) Standards with ubiquinol bulk, including an acute toxicity study and subchronic toxicity studies in rats and dogs, as well as in vitro and in vivo genotoxicity studies.

1.1. Review of previously unpublished studies

In the acute toxicity study in rats, groups of 5 male and 5 female rats were given a single oral dose of either 0, 2500, or 5000 mg/kg ubiquinol dissolved in corn oil and then evaluated for morbidity and mortality for the next 14 days. No abnormal clinical signs or significant differences from the control group in body weight were noted in treated animals (Oda, 2003).

In 13-week subchronic toxicity studies in rats, groups of 10 male and 10 female rats were given a daily dose of 0, 300, 600, or 1200 mg/kg of ubiquinol dissolved in corn oil for 13 weeks. No deaths occurred in any group during the study period. No abnormalities in general condition, body weight, food consumption, ophthalmological examination, or urinalysis were observed. Evaluation of hematological parameters revealed statistically significant prolongations of PT and APTT in males of the ubiquinol 1200 mg/kg group. However, these prolongations of PT and APTT were considered of little toxicological significance since they were slight and there were no changes suggestive of hemorrhage in the other examinations performed, including pathologic examination. Blood chemistry examination revealed elevated levels of ASAT (GOT) activity in females of the ubiquinol 300 and 1200 mg/kg groups, elevated levels of ALAT (GPT) activity in females in the ubiquinol 300 mg/kg and higher groups, and elevated LDH activity in females of the ubiquinol 300 and 600 mg/kg groups. Such changes are suggestive of adverse effects on the liver. Pathologic examination revealed test article-related effects on the liver, spleen, and mesenteric lymph nodes in females. In the liver, on histopathologic examination, microgranulomas, focal necrosis, or accumulation of macrophages, as well as fine vacuolation of hepatocytes and vacuolation of Kupffer cells were observed in each ubiquinol group. Liver weight was increased or tended to be increased. However, these changes were considered due to uptake of the administered ubiquinol by the liver, as an adaptive response to a xenobiotic compound, and the microgranulomas and focal necrosis were considered the result of excessive uptake of ubiquinol, which exceeded the capacity for adaptive response. These conclusions were based on the finding of localization to the liver of concentrated coenzyme Q_{10} dissolved in lipoproteins, as suggested by the positive reaction of the liver cells to oil red O staining for lipids on histological examination and by extremely high concentrations of total coenzyme Q_{10} in the liver, more than 8 mg/g detected on HPLC analysis, together with the previous finding by Mohr et al. (1992) and Tomasetti et al. (1999) that ubiquinol is extremely lipophilic and readily distributes into lipoproteins. Furthermore, in females, spleen weight was increased in the ubiquinol 600 mg/kg and higher groups, and accumulation of macrophages was observed in the spleen and mesenteric lymph nodes in each ubiquinol group. As in the liver, all of these effects were considered to be secondary effects following uptake of ubiquinol. Based on these findings, the no-observed-adverse-effect level (NOAEL) under the conditions of this study was estimated to be 600 mg/kg/day for males and less than 300 mg/kg/day for females (Kitano et al., submitted-a).

In light of changes in the clinical chemistry and histopathology observed in females of the 300 mg ubiquinol/kg/day and higher groups in the previous study (Kitano et al., submitted-a), a second 13-week oral toxicity study was conducted in female rats in order to determine NOAEL for ubiquinol in female rats (Kitano et al., submitted-a). Groups of 10 female rats were given a daily dose of 0, 75, 150, 200, or 300 mg/kg of ubiquinol dissolved in corn oil for 13 weeks. No death occurred in any group during the study period. No abnormalities in general condition, body weight, food consumption, ophthalmology examination, urinalysis, or hematology were observed. No dose-related or toxicologically significant changes in absolute or relative organ weights were observed. Evaluation of clinical chemistry parameters revealed somewhat elevated ASAT (GOT) activity in the ubiquinol 300 mg/kg group, which may be