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Effect of egg yolk phospholipids plasma elimination and tissue distribution of coenzyme Q_{10} administered in an emulsion to rats

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When coenzyme Q_{10} (CoQ_{10}) in fat emulsion emulsified with egg yolk phospholipids (PL) was administered intravenously to rats, CoQ_{10} was eliminated more rapidly than when it was solubilized with a polyoxyethylene derivative of hydrogenated castor oil. Although CoQ_{10} in emulsion form is distributed mainly to liver, increase of PL concentration in the emulsion increased the distribution of CoQ_{10} to heart which is a target organ for CoQ_{10}.

Since a fat emulsion that can be administered intravenously has become available, its use, or that of similar emulsions, as an intravenous or other parenteral vehicle for lipophilic drugs has been reported. Cyclandelate and nitroglycerol in emulsion form have been claimed suitable for intravenous administration (Jeppsson & Ljungberg 1973) and diazepam in an emulsion has lower toxicity, but equal anticonvulsant activity, to the commercial injection formulation (Hoffman-LaRoche & Co.) (Jeppsson & Ljungberg 1975). Moreover, a commercially available fat emulsion (Intralipid; Cutter Laboratories, Inc., California) has been reported to be a suitable intravenous vehicle for water-insoluble drugs (Fortner et al 1975). Recently, corticosteroid esters and indomethacin ester incorporated in fat emulsion were reported to show greater anti-inflammatory activities since small-sized emulsion particles can be taken up more easily into inflammatory cells (Mizushima et al 1982, 1983). As for the effect of emulsifier on drug elimination from blood, Jeppsson & Rossner (1975) reported that the elimination rate constants of lipid particles of emulsion were extensively affected by the composition of the emulsifying agents, while elimination rate constants of secobarbital and thiopental in emulsions were only slightly decreased from those of the drugs in aqueous solution after the drugs had been administered intravenously to rabbits. Later, Jeppsson (1976) reported that the plasma elimination patterns of diazepam in dogs and rabbits were not different between the emulsion and an ethanol-propylene glycol solution, both of which were administered intravenously as a vehicle for diazepam. As for drug distribution into tissues, Litterst et al (1974) reported that only bile and fat showed a vehicle-dependent change in distribution after lomustine was administered to rabbits intravenously in three formulations, i.e. ethanol-propylene glycol, ethanol-fat emulsion and ethanol-polyethoxylated vegetable oil emulsion. We now report an interesting effect of egg yolk phospholipids (PL) as an emulsifier on drug distribution to various tissues as well as drug elimination rates from plasma. Coenzyme Q_{10} (CoQ_{10}), which is used for improvement of congestive heart failure and angina pectoris, was chosen since it is highly lipophilic.

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Materials and methods

Soybean oil (Wako Pure Chemical Industries, Ltd, Tokyo), a polyoxyethylene derivative of hydrogenated castor oil (HCO-60; a gift from Nikko-Chemical Co., Tokyo) and egg yolk phospholipids (PL) (a gift from QP Co., Tokyo) were used without further purification. All-*trans*[3′-^{14}C]coenzyme Q_{10} ([^{14}C]-CoQ_{10}) (7·95 μCi mg^{-1}) kindly supplied by Eisai Co., Tokyo, showed over 99% purity as determined by thin layer chromatography according to Yuzuriha et al (1983). All other chemicals and reagents were of analytical grade or better.

[^{14}C]CoQ_{10} was dissolved in soybean oil (10 mg g^{-1} oil) and 1 g of this, the appropriate amount of PL and 250 mg of glycerol, were added to the sufficient water, and then emulsified for 2 min in a ice-cold bath with a sonicator (100 W: 5202 PZT, Ohtake Co., Tokyo). The emulsion volume was adjusted to 10 ml with water and then emulsified again for 1 min. The prepared emulsions were denoted as PL 1·2%, PL 12% and PL 24% corresponding to the PL concentrations in the emulsions. It was observed by optical microscopy that the PL 1·2% emulsion had particles about 1 μm diameter, while the PL 12 and 24% emulsions had particles smaller than 1 μm diameter on average. HCO-60 aqueous solution (0·7%) was used to solubilize [^{14}C]-CoQ_{10} at 1 mg ml^{-1}.

Male Wistar rats 230–280 g were used after being fasted overnight. Under light ether anaesthesia, each rat was cannulated with a polyethylene tube (PE 50: Clay Adams Co.) into the femoral artery and vein. After recovery, the rats had [^{14}C]CoQ_{10} (0·6 mg kg^{-1}) either as in emulsion or solubilized, administered via the femoral vein. Blood was collected through the femoral artery into heparinized micro-test tubes at appropriate times for 120 min. Plasma was obtained by centrifugation. At 120 min rats were decapitated, the blood washed out by perfusion with 0·9% NaCl and tissues removed for assay.

[^{14}C]CoQ_{10} in plasma and tissues was assayed using a liquid-scintillation counter (Aloka LSC-903, Tokyo) with a scintillation counting solution (10 g of 2,5-

Table 1. Coenzyme Q_{10} (CoQ_{10}) concentrations (μg g^{-1} tissue) in various rat tissues at 120 min after intravenous administration of 0·6 mg kg^{-1} of [^{14}C]CoQ_{10} either solubilized with HCO-60[a] or as emulsions with PL[b]. Values are expressed as mean ± s.d. from 3–4 experiments.

Dosage forms	Plasma[c]	Brain[c]	Lung	Heart[c]	Liver[c]	Spleen[c]	Kidney[c]
HCO-60 solution	9·05 ± 0·41	0·11 ± 0·02	1·46 ± 0·60	0·63 ± 0·03	1·14 ± 0·14	4·54 ± 1·49	0·63 ± 0·11
PL 1·2% emulsion	0·11 ± 0·01	0·01 ± 0·01	1·63 ± 0·40	1·29 ± 0·11	8·29 ± 1·06	18·5 ± 3·9	0·16 ± 0·05
PL 12% emulsion	0·21 ± 0·11	0·02 ± 0·01	1·32 ± 0·57	1·83 ± 1·15	7·81 ± 1·17	26·6 ± 13·1	0·13 ± 0·01
PL 24% emulsion	0·33 ± 0·02[d]	0·02 ± 0·01	3·11 ± 1·16	3·68 ± 1·16[d]	7·21 ± 1·17	22·1 ± 6·7	0·11 ± 0·03

[a] Polyoxyethylene derivative of hydrogenated castor oil. [b] Egg yolk phospholipids. [c] Different between HCO-solution and PL 1·2% emulsion ($P < 0·01$). [d] Different between PL 1·2% emulsion and PL 24% emulsion ($P < 0·05$).

diphenyloxazole and 0·5 g of 1,4-bis{2-(5-phenyloxalolyl)}-benzene in 1000 ml of toluene) after plasma or tissues had been oxidized to $^{14}CO_2$ (Aloka ASC-111).

Results and discussion

As shown in Fig. 1, CoQ_{10} administered in emulsion form was eliminated much more rapidly for the initial 30 min than when solubilized, it then almost reached a plateau after 60 min. The elimination rates of CoQ_{10} from the emulsions decreased as the concentration of PL increased. The distributions of CoQ_{10} in various tissues at 120 min are listed in Table 1. Those in liver and spleen increased, suggesting that little CoQ_{10} in emulsion escaped into plasma and that it was taken up by the reticuloendothelial system. This explains the results in Fig. 1 where CoQ_{10} in emulsion form was eliminated rapidly from plasma. The other tissues that showed significantly different levels between solubilized and emulsion forms were heart, kidney and brain. That CoQ_{10} in the emulsions was distributed to a greater extent to the heart than the solubilized form, is consistent with the report that soybean emulsion is removed in the myocardium as well as in the splanchnic region (Rossner 1974). On the other hand, CoQ_{10} in the emulsion became distributed to kidney and brain to a lesser extent than the solubilized form. This suggests that CoQ_{10} in emulsions is prevented from being excreted by the kidney and from being taken through the blood-brain barrier.

As the PL concentration in the emulsions increased, CoQ_{10} distribution to heart increased while its distribution to liver and kidney decreased. But the effect of PL concentration on the distribution to the brain was not seen. The effect on the distribution to spleen was not clear.

In conclusion, the differences of CoQ_{10} elimination and tissue distribution were clearly indicated between its solubilized form and the PL emulsions. The finding that increasing the PL concentration in the emulsion tended to decrease the distribution of CoQ_{10} to liver and spleen while increasing it to heart, suggests that CoQ_{10} in an emulsion of high PL concentration has potential as a means of treating heart conditions.

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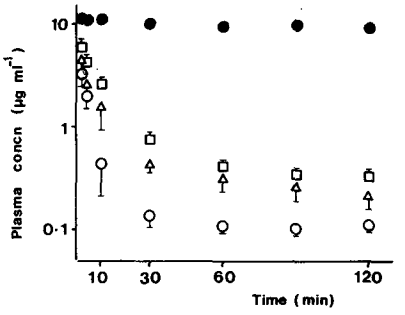

FIG. 1. Plasma concentration time courses in rats of coenzyme Q_{10} (CoQ_{10}) after intravenous administration of 0·6 mg kg^{-1} of [^{14}C]CoQ_{10} either solubilized with HCO-60 (a polyoxyethylene derivative of hydrogenated castor oil) or in emulsions made with PL (egg yolk phospholipids). The bars give the s.d. which for the solubilized preparation were within the symbol size. ● HCO-60; ○ PL 1·2% emulsion; △ PL 12% emulsion; □ PL 24% emulsion.

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