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ESTIMATION OF THE LINEARITY OF UBIDECARENONE PHARMACOKINETICS AFTER INTRAVENOUS ADMINISTRATION

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The dynamics of ubidecarenone (coenzyme Q_{10}) levels in rat blood plasma and liver were monitored for two days after i.v. injection of solubilized ubidecarenone at doses of 10 and 30 mg/kg. The kinetic curves of the drug in plasma were exponential for both doses. The areas under the concentration—time curves differed by 8.6 times for the 10 and 30 mg/kg doses. Normalization to the dose did not superimpose them. The drug accumulated gradually in liver with the areas under the concentration—time curves differing by a factor of 4.4. These data indicated that ubidecarenone pharmacokinetics in plasma and liver were nonlinear after intravascular injection.

Keywords: pharmacokinetics, coenzyme Q_{10}.

The cardio- and neuroprotective effectiveness of ubidecarenone (coenzyme Q_{10}) was demonstrated in numerous experimental and clinical investigations [1, 2]. The need to develop ubidecarenone dosage forms for parenteral and, primarily, i.v. administration for application in urgent situations (ischemic damage, myocardial infarct) has now become obvious. Pharmacokinetic studies are an important phase of preclinical trials of a new drug dosage form. The goal of this pilot study was to estimate the linearity of ubidecarenone pharmacokinetics after i.v. injection.

EXPERIMENTAL PART

The studies used male Wistar rats (250 – 300 g). The dynamics of coenzyme Q_{10} tissue levels were studied after i.v. injection of a solution of solubilized ubidecarenone (Kudesan® drops for internal use, 3%, OOO Vneshtorg Farma) at doses of 10 and 30 mg/kg. Samples of rat blood plasma and liver were collected during 48 h after the injection using 4 – 9 animals for each time point. The coenzyme Q_{10} baseline level was measured by collecting tissue samples from control animals after injection of normal saline. The coenzyme Q_{10} contents in the samples were measured by HPLC with electrochemical detection [3]. Areas under concentration–time curves (AUC_{0-48}) were calculated by a trapezoid method.

Statistical processing used the Statistica 6.0 software. Results were given as the average ± standard deviation. The Mann–Whitney U-criterion was used to compare groups. Differences were considered statistically significant for $p < 0.05$.

RESULTS AND DISCUSSION

Figure 1 shows ubidecarenone kinetic curves after i.v. injection at two doses. The coenzyme Q_{10} blood plasma levels were elevated through the whole observation period and exceeded the control levels by 200 and 850 times (for the 10 and 30 mg/kg doses, respectively) by 48 h. The data plotted in semi-logarithmic coordinates (Fig. 1*b*) demonstrated the exponential nature of the concentration decrease in the studied time interval. The areas under the concentration—time curves (Fig. 1*a*) for the 10 and 30 mg/kg doses differed by 8.6 times, not 3 times. Furthermore, normalization of the kinetic data to the dose did not superimpose the concentration—time curves (Table 1). These results indicated that the coenzyme Q_{10} pharmacokinetics were non-linear.

The non-linearity of ubidecarenone kinetics after *per os* administration was due to limited absorption in the gastroin-

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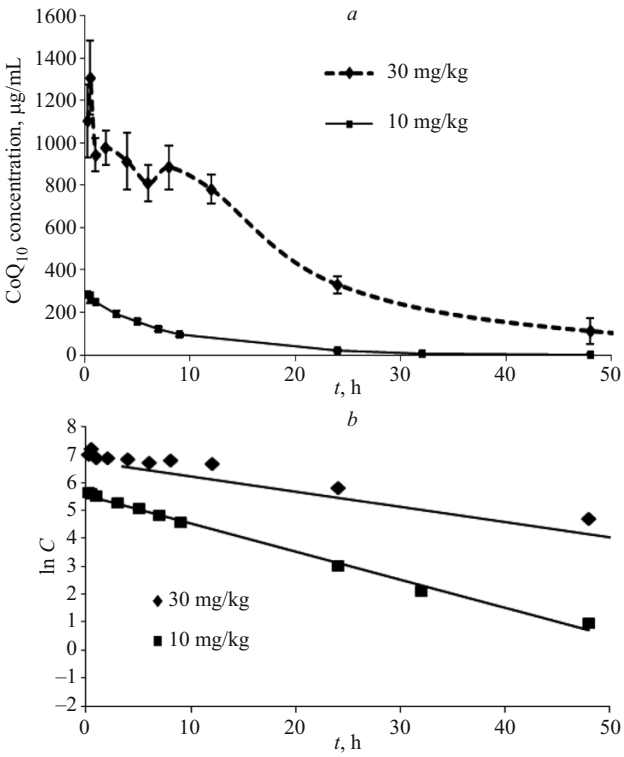

Fig. 1. Ubidecarenone kinetic curves for blood plasma of rats injected i.v. at doses of 10 (lower curve in both plots) and 30 mg/kg (upper curve in both plots): in coordinates of concentration—time (*a*) and ln(concentration)—time (*b*) (a trend line is given for each concentration).

TABLE 1. Areas Under Concentration—Time Curves (AUC_{0-48}, μg · h/mL) for Plasma and Liver After i.v. Injection of Coenzyme Q_{10}

Dose, mg/kg	AUC_{0-48} plasma*	AUC_{0-48} liver*
10	2620	5256
30	22658	23253
Normalized to the 10 mg/kg dose	7553	7751

* Calculated from average group concentrations for each time point.

testinal tract [4]. The non-linear coenzyme Q_{10} pharmacokinetics after i.v. injection in our investigation may have resulted from the particulars of its *in vivo* distribution. The liver is the main organ for accumulation and excretion of ubidecarenone and also for its secretion into the systemic circulation [4]. Figure 2 shows the accumulation dynamics in

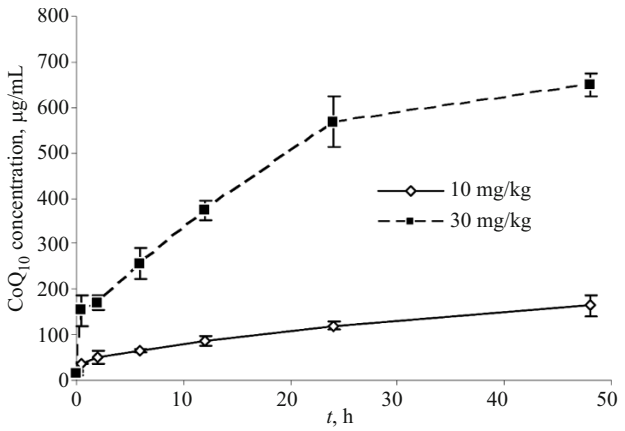

Fig. 2. Ubidecarenone accumulation dynamics in rat liver after i.v. injection at two doses. The CoQ_{10} concentration at each time point exceeded statistically significantly the control level ($p < 0.01$). Upper curve, 30 mg/kg dose; lower curve, 10 mg/kg dose.

liver of coenzyme Q_{10} after administration at two doses. The concentration increased fastest in the first hours after the injection and slowed considerably after the first day. Thus, ubidecarenone after i.v. injection was distributed for at least 48 h. Tripling the dose increased the area under the liver concentration–time curve by 4.4 times. The significant amount of coenzyme Q_{10} accumulated in the liver could provide a long-term source for periodic replenishment of its plasma levels and produce a characteristic kinetic profile (several ubidecarenone concentration peaks in plasma for the larger dose, Fig. 1*a*).

The results indicated that ubidecarenone pharmacokinetics were non-linear in plasma and liver after i.v. injection.

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