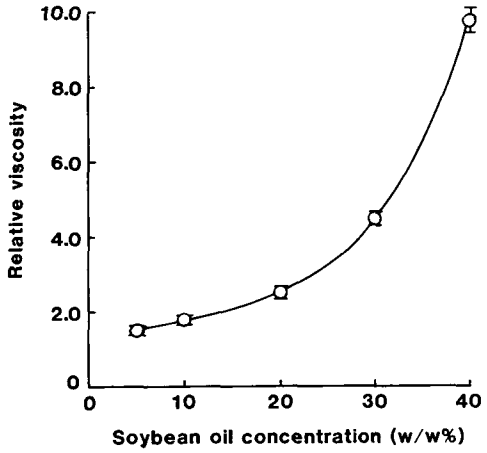

FIG. 6. Effect of oil phase volume on relative viscosity of emulsion prepared with 1·2% (w/w) egg lecithin.

the system. As demonstrated in Fig. 3, at lower concentrations of 0·6–1·2% (w/w) egg lecithin, the adsorbed layer around the emulsion droplets formed, decreasing the particle size. At higher concentrations of egg lecithin (above 1·6% (w/w)), the surplus egg lecithin molecules associated to form micelles or vesicles, increasing the volume ratio between the dispersed phase and the continuous phase.

Intravascular administration of a viscous preparation is associated with pain (Korttila et al 1976); accordingly, we investigated the rheological properties of emulsions by changing the oil volume ratio of the dispersed phase. Fig. 6 shows the effect of oil phase volume on the relative viscosity of emulsions. This increased as the oil phase volume ratio to the continuous phase increased. These results strongly suggest that the interaction between oil droplets in emulsions increases due to their closer approach in the continuous phase.

In conclusion, it appears that lecithin as an emulsifier is effective at 1·2% (w/w) for the preparation of intravenous fat emulsions, at least in terms of the physicochemical parameters and surface properties determined here.

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The effect of chronic captopril administration on hepatic blood flow of the rat

SIMON BAR-MEIR, HAIA PRIGOJIN, RAFAEL BRUCK, ZIPORA KREPEL, YONA AVNI, *Department of Gastroenterology, Edith Wolfson Hospital, Holon and Sackler School of Medicine, Tel Aviv University, Israel*

Abstract—The effect of chronic captopril administration on indocyanine green (ICG) clearance and hepatic extraction has been studied in the rat using the intact liver for ICG clearance and the isolated perfused liver for ICG extraction. The captopril was added to the drinking water to give a calculated daily intake from 0·45 mg kg^{-1}. Hepatic clearance of ICG was dose related from $16·5 \pm 2·4$ (control) to $7·2 \pm 1·6$ mL min^{-1} kg^{-1}, respectively. The hepatic extraction of ICG was not significantly different ($37 \pm 6\%$) from the control value in groups on 4 and 45 mg kg^{-1} daily. Since ICG clearance and extraction are dependent on hepatic blood, a change in ICG clearance without a change in the extraction reflects a similar change in the hepatic blood flow. This remained unchanged at daily captopril intakes of 1 and 4 mg kg^{-1} and decreased when the daily intake was 10 mg kg^{-1} or higher. If these results in the rat are applicable to man, the chronic administration of therapeutic doses of captopril (0·5–2 mg kg^{-1}) will not affect the hepatic blood flow.

Correspondence to: S. Bar-Meir, Department of Gastroenterology, Edith Wolfson Hospital, Holon 58100, Israel.

Captopril, an oral angiotensin converting enzyme inhibitor, is used in the treatment of hypertension and congestive heart failure (MacGregor et al 1979). Clinical and experimental studies suggest that it lowers total systemic vascular resistance by inducing selective vasodilatation in regional vascular beds (Cavras et al 1978; Faxon et al 1980, 1981). Animal studies have shown that it increases renal, cerebral and coronary blood flow at the expense of hepato-mesenteric, cutaneous and skeletal muscle perfusion (Cavras et al 1978).

Crossley et al (1984) found a decrease in hepatic blood flow following the administration of 50–100 mg of captopril to hypertensive patients while Eriksson et al (1984) and Shepherd et al (1985) did not find any effect of the drug on hepatic blood flow in patients with liver cirrhosis and in normal volunteers. In those three studies only single doses of captopril were given; no information is available on the effect of chronic administration of captopril on hepatic blood flow. We have investigated the effect of chronic captopril administration in the rat.

Materials and methods

Wistar rats, 250–300 g, were divided into 6 groups of 6 animals. All were fed with ordinary chow, and had free access to tap water alone or containing captopril at concentrations of 0·4, 0·28, 0·09, 0·04 and 0·01 mg mL^{-1}. Each of the rats drank daily 30–40 mL of water corresponding to captopril intakes of 0, 45, 30, 10, 4 and 1 mg kg^{-1} day^{-1}, respectively. The captopril solutions were freshly prepared every other day.

Estimation of indocyanine green (ICG) clearance. After twenty one days of captopril administration the animals were anaesthetized with chloral hydrate (400 mg kg^{-1}) and ICG dissolved in 0·9% NaCl with 4% bovine serum albumin was administered intravenously into the tail vein at a rate of 31·7 μg min^{-1} for 60 min using a syringe driver (Ms 16 Grasby dynamics). To verify that serum ICG achieved a steady state concentration (Smith & Struyker-Boudier 1986), ICG was determined at 60, 65 and 70 min.

Blood clearance (CL) was determined as:

$$CL = \text{infusion rate}/C_{ss}.$$

Where C_{ss} is blood concentration of ICG at a steady state. Blood concentration was calculated as:

Blood concentration =
serum concentration × (1-haematocrit).

Serum ICG concentration was determined by spectrophotometry (wavelength: 805 nm) using pooled serum as a zero reference.

Estimation of ICG hepatic extraction. Rats were killed two days after the determination of ICG clearance, and ICG extraction was determined using the isolated perfused liver as previously described (Bruck et al 1988). Briefly, rat livers were perfused in-situ via the portal vein with oxygenated, non-recycling Krebs-Ringer bicarbonate buffer, containing 20% washed human erythrocytes, 4 g L^{-1} glucose and 20 g L^{-1} bovine serum albumin. A roller pump circulated perfusate through the liver at a fixed flow rate of 10–12 mL min^{-1}. Perfusate temperature, pH and pressure were monitored continuously and the preparation discarded if variations occurred outside the physiologic range. The extraction rate was determined in three groups — the control and the groups that received 4 and 45 mg captopril kg^{-1} day^{-1}, up to the time of death.

Statistical analysis was determined by Student's *t*-test; a *P* value of $< 0·05$ denoted statistical significance between groups.

Results

A dose response showing the effect of various dosages of captopril on ICG clearance and hepatic extraction is shown in Table 1. The extraction rate was not altered by the different dosages of captopril administered. The estimated hepatic blood flow remained unchanged at daily captopril intakes of 1 and 4 mg kg^{-1}. Only at doses of 10 mg kg^{-1} day^{-1} and above was a significant decrease in hepatic blood flow found.

Table 1. Hepatic clearance and extraction of ICG at different daily captopril intakes.

Captopril mg kg^{-1} day^{-1}	ICG clearance mL min^{-1} kg^{-1}	ICG extraction (%)
0	16·5 ± 2·4	37 ± 6
1	16·5 ± 1·6	—
4	15·4 ± 1·5	33 ± 3
10	13·8 ± 1·1*	—
30	11·6 ± 3·3**	—
45	7·2 ± 1·6***	33 ± 4

Data are expressed as mean ± s.d., n = 6.
* $P < 0·05$; ** $P < 0·005$; *** $P < 0·0005$.

Discussion

Chronic administration of captopril to rats was associated with a decrease in the hepatic blood flow only when 10 mg kg^{-1} day^{-1} or more was given. This is substantially beyond the therapeutic doses in man (0·5–2 mg kg^{-1}).

The reduction in hepatic blood flow at high doses of captopril was not due to a change in the systemic blood pressure since it has already been shown over that dose range that the systemic blood pressure does not change (Podjarny et al 1988). This was also our experience in captopril treated rats where blood pressure was measured.

The three weeks of captopril intake was also chosen by other authors as the appropriate time for the study of the effect of chronic captopril administration in the rat. During that period, urine output and water intake increased as a result of the drug's effect on the kidneys (Podjarny et al 1988). If our results in the rat are applicable to man, the chronic administration of therapeutic doses of captopril should not affect hepatic blood flow.

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