(+)-PROPRANOLOL CLEARANCE, AN ESTIMATION OF HEPATIC BLOOD FLOW IN MAN

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1 Hepatic blood flow was determined before and during (+)- and (±)-propranolol plasma concentration plateaus in 19 patients with suspected renal hypertension and normal liver function.

2 Hepatic blood flow significantly decreased ($P < 0.001$) during (±)-propranolol administration and remained unchanged during (+)-propranolol administration.

3 Hepatic extraction ratio was $74 \pm 1\%$ for (±)-propranolol and $79 \pm 2\%$ for (+)-propranolol.

4 Total propranolol clearances were determined during the steady-state achieved by a constant infusion. A highly significant positive relationship was observed ($r = +0.86$; $P < 0.01$) between hepatic blood flow and (+)-propranolol clearance. The slope of the curve was 1.05 ± 0.27 .

5 The result implies that the total clearance of (+)-propranolol constitutes an accurate estimation of basal hepatic blood flow in subjects with normal liver function.

Introduction

Several methods have been proposed for the determination of the hepatic blood flow in man (see review in Benhamou, Sicot, Erlinger, 1971). Most of them require hepatic vein catheterization. This technique is not necessary when using substances with a high hepatic extraction ratio. In such conditions, total body clearance is highly sensitive to the alterations in hepatic blood flow (Rowland, Benet & Graham, 1973) and constitutes an indirect evaluation of hepatic blood flow.

Animal experiments have shown that propranolol is almost entirely cleared by the liver. In addition, (+)-propranolol does not seem to affect hepatic blood flow (Nies, Evans & Shand, 1972). Thus, this substance could be used to estimate hepatic blood flow in man. The purpose of the study was, in patients with permanent hypertension, (i) to evaluate the effect of (±)- and (+)-propranolol on hepatic blood flow, and (ii) to determine the hepatic extraction ratio. From the results, it will be proved that total (+)-propranolol plasma clearance constitutes a good estimation of hepatic blood flow in patients with normal liver function.

Methods

Patients

Nineteen hypertensive patients (12 men, 7 women) were included in the study. Mean $\pm$ s.e. mean age was

36 ± 3 years. All patients were untreated or had discontinued their therapy at least 2 weeks before the investigation. They were hospitalized and placed on a 110 mEq/day sodium diet. On the 3rd day of hospitalization, diastolic blood pressure was constantly above 90 mmHg. Extensive investigations included blood and urinary electrolytes, catechol amines determinations, timed intravenous urography and renal arteriography. Of the 19 patients, 13 had unilateral renal-artery stenosis, 6 unilateral small kidney. Mean creatinine clearance was 98 ± 4 ml min⁻¹ 1.73 m². No subjects had cardiac or neurologic involvement. All had normal values of transaminases, bilirubin, alkaline phosphatase and sulfobromophthalein clearance.

Haemodynamic investigation

The haemodynamic study was performed at 09.00 h, 3-8 days after hospitalization, in order to determine renal and peripheral venous plasma-renin activities and to estimate the hepatic blood flow. Consent for investigation was obtained in all patients after a detailed description of the procedure. Blood pressure and electrocardiograms were recorded repeatedly. No pre-medication was used. Three catheters were inserted into antecubital veins for infusion and blood withdrawal. A catheter was introduced via the right femoral vein by the Seldinger technique under fluoroscopic control. Each position of the catheter was verified by rapid injection of 2 ml radio-selectan.

Samples for plasma renin measurements were withdrawn from the inferior vena cava and both renal veins. All samples were taken after overnight recumbency.

The catheter was finally positioned in the right hepatic vein. Estimation of hepatic blood flow used a plasma concentration plateau of indocyanine green (ICG) (Bradley, Ingelfinger, Bradley & Curry, 1945; Caesar, Shaldon, Chiandussi, Guevara & Sherlock, 1961). This plateau (ICG concentration: 1.5 µg/ml; ranges: 1.1–1.8 µg/ml) was achieved within 30 min by means of an intravenous bolus of 20 mg followed by a constant infusion of the dye at a rate of 0.6 mg/min. Six paired peripheral and hepatic venous samples were taken at 5 min intervals for the estimation of basal hepatic blood flow. Thus, the determination of basal hepatic blood flow required about 75 min. The ICG infusion was continued throughout the remaining procedure to determine hepatic blood flow after propranolol administration.

After the determination of basal hepatic blood flow, propranolol was administered intravenously until steady-state concentration were achieved. The bolus size (0.27 mg/kg) and the continuous infusion rate (0.08 mg kg⁻¹ h⁻¹) were based on previous kinetic data (Weiss, Safar, Chevillard, Frydman, Lemaire & Alexandre, 1976). In all cases, higher initial levels declined rapidly within 30–45 min to the predetermined concentration which was maintained during the infusion period. (+)-propranolol was used in 7 cases and (±)-propranolol in 12 cases. Six serial paired peripheral and hepatic venous samples were then withdrawn during the steady state for propranolol and ICG determinations. For ICG and propranolol, the concentration was the mean value of the six samples. The reproducibility of the determination was 4 ± 2% for ICG and 6 ± 3% for propranolol. The infusion pump and the syringes were calibrated after each procedure.

Hepatic blood flow (HBF) was calculated from the formula:

$$HBF = \frac{Q}{(C_v - C_{hv})(1 - H_t)}$$

where Q was the ICG infusion rate, C_v and C_{hv} equal the mean value of the six peripheral and hepatic venous concentration measured at the steady state and H_t is the hepatic venous hematocrit. Total clearance of propranolol (TC) was estimated by TC = Q/C_v, where Q is propranolol infusion rate, and C_v the peripheral venous concentration. The hepatic extraction of propranolol represented the ratio of the concentration difference in the peripheral and hepatic venous blood to the peripheral venous concentration of the drug. HBF and TC were corrected for body weight.

Figure 1 Effect of (a) (±) and (b) (+)-propranolol on hepatic blood flow in individual hypertensive patients.

Biochemical determinations

The ICG and propranolol solutions were freshly prepared for each subject. ICG concentrations were estimated with a Beckman spectrophotometer according the classical method (Bradley *et al.*, 1945; Caesar *et al.*, 1961). Propranolol ((+)- or (±)-) was assayed fluorometrically by using Shand *et al.* method's (Shand, Nuckolls & Oates, 1970). It was verified that arterial and peripheral venous samples gave similar results. Propranolol concentrations were determined both in blood and plasma. The blood plasma ratio was 0.90 ± 0.03.

Results

Hepatic blood flow significantly decreased during (±)-propranolol infusion (P < 0.001) and remained unchanged during (+)-propranolol infusion (Figure 1).

Hepatic extraction was measured during plasma concentration plateaus of (+)- and (±)-propranolol. Mean concentration values were respectively 67 ± 7 ng/ml and 92 ± 9 ng/ml. Hepatic extraction was 79 ± 1% with (+)-propranolol and 74 ± 1% with (±)-propranolol (Figure 2). Results were not significantly affected when using blood determinations.

(+)- and (±)-propranolol clearances were both related to the basal hepatic blood flow. A direct correlation was found between (±)-propranolol

Figure 2 Hepatic extraction ratios of (a) (±) and (b) (+)-propranolol in individual hypertensive patients.

clearance and basal hepatic blood flow ($r=0.65$; $P<0.025$). However a more practical and better correlation was seen between (+)-propranolol clearance and hepatic blood flow ($r=0.86$; $P<0.01$). The slope of the curve was 1.05 ± 0.27 (Figure 3).

Discussion

Many substances, by virtue of a high hepatic extraction ratio, can be considered as flow-dependent and highly sensitive to changes in hepatic blood flow. Previous studies with aldosterone (Tait, Bougas, Little, Tait & Flood, 1965), ligocaine (Stenson, Constantino & Harrison, 1971), and oxyphenbutazone (Nies *et al.*, 1973) have determined relationship between changes in hepatic blood flow and total clearance of these substances. A high hepatic extraction ratio of (±)-propranolol has been demonstrated in monkeys, but mainly in dogs (Nies *et al.*, 1972). A nearly complete extraction has been also postulated to occur in man at relatively low drugs concentration (Nies *et al.*, 1972) and has suggested that propranolol might be added to the list of the flow dependent drugs.

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Figure 3 Relationship between hepatic blood flow and (+)-propranolol total plasma clearance. The equation is $y = 1.06x + 1.16$ ($y = ax + b$). Note that the b value is not significantly different from zero. $r = 0.86$, $P < 0.01$.

Our study confirms a high hepatic ratio of both (+)- and (±)-propranolol and demonstrates strong significant relationship between hepatic blood flow and the total clearance. A decrease in hepatic blood flow is produced by the β -adrenergic receptor blockade due to the (–)-isomer in the racemic mixture. On the other hand, (+)-propranolol has no haemodynamic effect. The slope of the hepatic blood flow-total (+)-propranolol clearance relationship is 1.05 ± 0.27 . Such a result provides evidence that the (+)-propranolol total plasma clearance constitutes a safe method for the estimation of hepatic blood flow in men with normal liver function.

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