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Effect of propranolol on portal vein hemodynamics: assessment by duplex sonography and indocyanine green clearance in healthy volunteers

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Summary. In the past decade several randomized trials have shown a beneficial effect of propranolol in cirrhotic patients. The effect of propranolol has been attributed to a reduction in portal vein pressure. So far the monitoring of portal vein hemodynamics following propranolol administration has been achieved mainly by hepatic vein catheterization. We studied the effect of propranolol on portal vein hemodynamics noninvasively in five healthy volunteers using duplex sonography and indocyanine green clearance. Measured by duplex sonography, blood flow was reduced by 28.6% in the portal vein ($P<0.05$) and by 8.7% in the hepatic artery (NS) 60 min after oral administration of 80 mg propranolol. During this time total hepatic blood flow, measured by indocyanine green clearance, was reduced by 19.5% ($P<0.05$). We conclude that both methods are useful for the study of portal vein hemodynamics during propranolol therapy, duplex sonography being more easily practicable.

Key words: Portal hypertension – Duplex sonography – Indocyanine green clearance – Propranolol

After the report of Lebrec in 1982 [17] several other clinical trials (see [13] for meta-analysis) confirmed a reduction in both mortality and frequency of bleeding episodes from esophageal varices in patients with liver cirrhosis following propranolol therapy. The beneficial effect of propranolol has been related to a reduction in portal pressure, probably through a decrease in cardiac output via β_1-receptors and through a vasoconstriction of splanchnic vessels via β_2-receptors [2, 21]. As the hemodynamic response to propranolol was found to be variable among cirrhotic patients, the identification and monitoring of the so-called propranolol responders (50–80%) was advocated [8]. In many studies the hemodynamic response to propranolol was assessed invasively by hepatic vein catheterization with measurements of the wedged and free hepatic venous pressures [11, 12].

This study investigated the hemodynamic response to propranolol in healthy volunteers by two noninvasive methods: duplex sonography for measurements of blood flow in the portal vein and hepatic artery, and indocyanine green (ICG) clearance for measurements of total hepatic blood flow.

Subjects and methods

Five healthy volunteers (two women, three men) aged 25 years were included in the study. The subjects gave oral informed consent, and the study protocol was approved by the local committee for human research. After fasting overnight and resting for 15 min the subjects underwent duplex sonography and ICG clearance test in a supine position according to following protocol: at time 0 (injection of ICG, oral administration of propranolol), after 60 min, and after 120 min duplex sonography was performed, and blood samples were taken for determination of propranolol and ICG plasma levels. Blood pressure and heart rate were checked at 15-min intervals. The procedure was performed with propranolol (80 mg) administered orally at time 0, the observer being blinded as to the medication which the subjects obtained.

Duplex sonography was performed on a Ultramark 5 (ATL) with 3.0 MHz imaging/Doppler transducer. After localization of the portal vein and the hepatic artery during a shallow breath, maximum (V_{max}) and mean (V_{mean}) velocity were determined by standard Doppler equation: $V = fd(t) \times c/2ft \times \cos$ @, where $fd(t)$ is the instantaneous mean Doppler shift, c the velocity of ultrasound in blood, ft the transmitted zero-crossing frequency, and @ the angle between the ultrasound beam and the blood vessel axis [6]. Blood

Abbreviation: ICG = indocyanine green

Table 1. Results of ICG measurements in healthy volunteers before and 1 h after propranolol

Patient	Sex	Age (years)	Plasma concentration of propranolol (ng/ml)	Plasma clearance ($ml\ kg^{-1}\ min^{-1}$)		Extraction rate (%)		Hepatic blood flow ($ml\ kg^{-1}\ min^{-1}$)	
				Before	After	Before	After	Before	After
1 J.Z.	M	29	37.42	8.10	6.61	63.5	61.3	22.0	18.4
2 E.N.	M	25	27.38	7.97	5.92	63.1	57.4	21.7	17.9
3 W.F.	W	25	16.72	7.73	6.16	61.4	60.4	20.0	16.7
4 M.K.	M	28	22.42	8.87	6.44	60.2	58.7	24.2	18.7
5 U.R.	W	26	22.18	8.80	7.20	57.0	58.7	26.4	20.8
Mean ± SD		26.6	25.22	8.29	6.47	61.0	59.3	22.9	18.5
		1.8	7.8	0.51	0.49	2.6	1.5	2.5	1.5
Difference[a] %					−22.0*		−2.8		−19.5*

* Significantly reduced, $P<0.05$
[a] Relative difference to baseline value before propranolol

flow was calculated by multiplying an average of three flow velocity measurements with the vascular cross-sectional area as shown by the real-time sonography [26].

For the determination of ICG clearance, a bolus dose of ICG (0.5 mg/kg) was administered in a cannulated antecubital vein. Immediately after ICG injection the vein was flushed with 1 ml heparinized saline (100 IE/ml). The concentrations of ICG in the blood samples taken at time 0 and after 60 min were measured by spectrophotometry. In preliminary studies kinetic data of intravenous ICG bolus injection (0.5 mg/kg) had been obtained. The plasma clearance was calculated according to the equation: Clp = dose/AUC (area under the plasma concentration-time curve) and the hepatic extraction ratio was calculated according to a two-compartment model [4, 10].

Propranolol plasma concentrations were measured by high-pressure liquid chromatography.

The differences in variables were analyzed using the Wilcoxon ranked test for paired samples.

Results

ICG clearance data are given in Table 1 and hemodynamic data in Table 2 and Fig. 1. With ICG clearance, baseline hepatic blood flow was measured at 1555 ml/min (1460–1650). Measured by duplex sonography, baseline portal blood flow was 684 ml/min (605–840) and baseline hepatic arterial blood flow 206 ml/min (121–236), yielding a total hepatic blood flow of 890 ml/min (822–1076).

One hour after oral administration of propranolol, hepatic blood flow measured by ICG clearance decreased by 19.5% ($P<0.05$) from 1555 to 1262 ml/min (1206–1380). During this time plasma clearance decreased by 22.0% ($P<0.05$) from 8.29 $ml\ kg^{-1}\ min^{-1}$ (7.73–8.87) to 6.47 $ml\ kg^{-1}\ min^{-1}$ (5.92–7.20) and the hepatic extraction ratio decreased by 2.8% (NS) from 61.0% (57.0–63.5) to 59.3% (57.4–61.3).

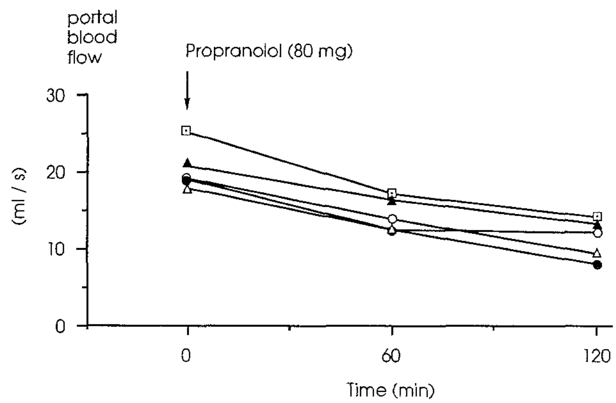

Fig. 1. Portal blood flow (ml/s) measured by duplex sonography in five healthy volunteers after the oral administration of 80 mg propranolol

One hour after oral administration of propranolol, portal blood flow measured by duplex sonography decreased by 28.6% ($P<0.05$) from 684 to 489 ml/min (417–579) and hepatic arterial blood flow decreased by 8.7% (NS) from 206 to 188 ml/min (113–236).

Two hours after oral administration of propranolol, portal blood flow measured by duplex sonography decreased by 42.9% ($P<0.05$) from 694 to 391 ml/min (303–479) and hepatic arterial blood flow decreased by 14.1% (NS) from 206 to 177 ml/min (130–224).

One hour after oral administration of propranolol, systolic blood pressure decreased by 7.2% ($P<0.05$) from 125 (115–130 to 116 mmHg (110–124), diastolic blood pressure decreased by 11.5 ($P<0.05$) from 78 (69–85) to 69 mmHg (64–73),

Table 2. Hemodynamic and duplex sonographic changes under 80 mg propranolol in healthy volunteers ($n=5$)

	Before propranolol	1 h after propranolol	2 h after propranolol
Plasma concentration of propranolol (ng/ml)	0.0	25.22±7.8	34.86±11.3
Blood pressure (mmHg)	125/78±6.2/6.1	116/69±5.2/4.1 (−7.2%*/−11.5%*)	110/69±3.6/4.2 (−12.0%*/−11.5%*)
Heart rate (bpm)	67±5.3	55±6.8 (−17.9%*)	49±3.2 (−26.9%*)
Portal vein			
V_{max} (cm/s)	28.1±2.0	20.5±2.8 (−26.8%*)	15.9±1.9 (−43.5%*)
V_{mean} (cm/s)	15.6±1.1	11.4±1.4 (−26.8%*)	8.8±1.0 (−43.5%*)
Diameter (cm)	0.97±0.10	0.97±0.11 (0%)	0.96±0.08 (−1.0%)
Blood flow (ml/min)	684±94	489±75 (−28.6%*)	391±88 (−42.9%*)
Hepatic arterty			
V_{max} (cm/s)	59.4±10.5	49.4±7.6 (−16.8%*)	46.8±8.7 (−21.2%*)
V_{mean} (cm/s)	18.6±2.1	17.0±2.1 (−8.6%)	16.0±2.5 (−14.0%)
Diameter (cm)	0.48±0.04	0.48±0.04	0.48±0.04
Blood flow (ml/min)	206±50	188±47 (−8.7%)	177±47 (−14.1%)

* Significantly reduced $P<0.05$
Figures in parentheses, relative difference to baseline value before propranolol

and heart rate decreased by 17.9% ($P<0.05$) from 67 (61–75) to 55 beats/min (48–66). The mean propranolol plasma concentration was 25.2 ng/ml (16.7–37.4).

Two hours after oral administration of propranolol, systolic blood pressure decreased by 12% ($P<0.05$) from 125 to 10 mmHg (106–114), diastolic blood pressure decreased by 11.5% ($P<0.05$) from 78 to 69 mmHg (65–73), and heart rate decreased by 26.9% ($P<0.05$) from 67 to 49 beats/min (46–52). The mean propranolol plasma concentration was 34.9 ng/ml (23.6–46.2).

Discussion

In the past few years the combination of ultrasonography and pulsed Doppler flowmeter (duplex sonography) has been employed with success for noninvasive measurements of portal blood flow [19]. The reproducibility of duplex sonography is high, and a close correlation with the results of cineangiographic measurements has been demonstrated [22]. This new technique has proven accurate for the hemodynamic evaluation of portal blood flow [7, 20, 21, 24].

Duplex sonography measurements of portal blood flow (684 ml/min) and hepatic arterial blood flow (206 ml/min) in our healthy volunteers corresponded to the values reported in the literature [3, 5, 22]. In this study of healthy volunteers, portal blood flow measured by duplex sonography was uniformly reduced by 28.6% ($P<0.05$) 60 min and by 42.9% ($P<0.05$) 120 min after the administration of 80 mg propranolol. The reduction is comparable with the 23–28% reduction in hepatic venous pressure gradient reported in French studies on cirrhotic patients [17]. Other studies found a more variable portal pressure response to propranolol, with a lack of relationship between the response to propranolol and the severity of liver disease [2, 8, 23, 25]. These findings lead to the classification as responders and nonresponders. So far there is no clear explanation for the variable portal pressure response to propranolol. Neither propranolol plasma levels nor heart rate reduction were useful in assessing portal pressure response [8], and the use of hepatic vein catheterization has been proposed in patients treated with propranolol, as a decrease in the hepatic venous pressure gradient to 12 mmHg or less was found to be a good prognostic indicator [12].

In this study, hepatic arterial blood flow measured by duplex sonography was not significantly reduced after propranolol (8.7%). This is consistent with the currently postulated mechanism by which propranolol decreases portal pressure: principally through a reduction in blood inflow into the portal system (via splanchnic β_2-receptors) and only secondary through a reduction in blood inflow into the hepatic artery due to a reduction in cardiac output (via cardial β_1-receptors) [16].

Total hepatic blood flow measurements calculated by ICG clearance (1555 ml/min) were also consistent with data from the literature. However, there was a discrepancy with the total blood flow measurements obtained by duplex sonography (890 ml/min). The reduction in total hepatic blood flow after propranolol measured with ICG clearance (19.5%) was also lower than the reduction measured with duplex sonography.

The discrepancy between the measurements could arise from limitations of the employed methods. It is known that duplex sonography may overestimate real blood flow by up to 33% because of incorrect measurements of the Doppler shift, the cross-sectional area of the portal vein, and the angle between flow axis and transducer axis. The limitations of duplex sonography are described in detail elsewhereare and are especially applicable to acutely ill and uncooperative patients [9, 15, 18].

The clearance of ICG from plasma has been used for 30 years to estimate hepatic blood flow [1, 14]. The assumption inherent in measuring ICG clearance is that systemic ICG clearance is equal to liver blood flow only if ICG is cleared only by the liver, and if the calculated extraction ratio is correct. However, the exact determination of the extraction ratio and the amount of temporary extrahepatic distribution of ICG has not been solved unequivocally by experimental studies, and a possible overestimation of portal blood flow by 20–30% must be taken into account [3]. Using a two-compartment model, the calculated extraction ratios in this study (61%) were consistent with the data published by Burczynski et al. (65%) [3].

As no invasive method was used in this study as control, it cannot be decided which of the employed methods, duplex sonography or ICG clearance, is more accurate for the study of portal vein hemodynamics after propranolol therapy. Evidently a major advantage of duplex sonography in clinical practice is that it is easily available and completely noninvasive.

In summary, the influence of 80 mg propranolol on hepatic blood flow can be registered both with duplex sonography and ICG clearance in healthy volunteers. Regarding technical limitations, duplex sonography and ICG clearance may be used more intensively in the study of the hemodynamic response of propranolol in cirrhotic patients.

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