BRIEF COMMUNICATION

Sildenafil Has No Effect on Portal Pressure but Lowers Arterial Pressure in Patients With Compensated Cirrhosis

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BACKGROUND & AIMS: The reduction of portal pressure in patients with early compensated cirrhosis may be more responsive to drugs increasing intrahepatic vasodilatation than those reducing portal venous inflow. The phosphodiesterase-5 (PDE-V) inhibitor sildenafil can potentially reduce portal pressure by decreasing intrahepatic resistance, but its systemic vasodilatory effects may be deleterious. The aim of this study was to evaluate the effect of sildenafil on systemic and portal hemodynamics in an open-label pilot study. **METHODS:** Twelve patients with compensated cirrhosis and baseline hepatic venous pressure gradient (HVPG) >5 mm Hg received 25 mg of oral sildenafil. Mean arterial pressure (MAP), heart rate (HR), and HVPG were repeated after 30 and 60 minutes in 9/12 patients at 90 minutes (after an additional 25 mg of sildenafil). HVPG tracings were read by 3 blinded observers. **RESULTS:** All 12 patients were Child A with median MAP of 92 mm Hg (interquartile range, 83–94) and HVPG 10.4 mm Hg (interquartile range, 6.6–13.0). While MAP decreased significantly at all time points, sildenafil had no effect on HVPG. **CONCLUSIONS: As shown with other vasodilators in compensated cirrhotic patients, sildenafil at therapeutic doses for erectile dysfunction reduces MAP without reducing portal pressure. The search should continue for specific intrahepatic vasodilators.**

Keywords: Portal Hypertension; Phosphodiesterase-V Inhibitor; HVPG.

Portal hypertension is the major cause of morbidity and mortality in patients with cirrhosis. Portal hypertension is initially due to increased intrahepatic resistance and subsequently maintained by an increase in portal blood inflow. A reduction in portal pressure results in a lower rate of complications of cirrhosis.[1–3]

Nonselective beta blockers (BB) reduce portal pressure by reducing portal venous inflow. Although BB prevent variceal hemorrhage in patients with varices they do not prevent the development of varices,[4] perhaps because portal hypertension in patients without varices (early disease) is more dependent on increased intrahepatic resistance than increased portal inflow. Experimental studies have demonstrated that cirrhotic rats without ascites already have impaired intrahepatic vasorelaxation.[5]

Because portal pressure reduction in patients with early (compensated) cirrhosis is related to a decrease in outcomes,[4] pharmacological therapy should be targeted at reducing intrahepatic resistance by increasing intrahepatic nitric oxide (NO). Available vasodilators not only reduce intrahepatic resistance but also have a systemic effect that reduces mean arterial pressure (MAP). This is potentially deleterious, particularly for patients with more advanced cirrhosis who are already vasodilated.

Increased phosphodiesterase-5 (PDE-V) expression is involved in the decreased vasodilator response to NO in cirrhotic rat livers.[6] This has raised the possibility that PDE-V inhibitors, which also exert their effects through NO, may have a beneficial intrahepatic vasodilatory effect.

PDE-V inhibitors (PDEI) such as sildenafil, accentuate the vascular smooth muscle relaxation effects of NO by maintaining high levels of cyclic guanosine monophosphate (cGMP).[7,8] Studies of PDEI for portal hypertension have shown conflicting results, perhaps because they include patients with both compensated and decompensated cirrhosis.[9–11] The objective of this study was to establish the portal and hemodynamic effects of sildenafil specifically in patients with compensated cirrhosis.

Methods

Patients

This was an open-label prospective single center pilot study. Patients with compensated cirrhosis between 18 and 75 years with a hepatic venous pressure gradient (HVPG) >5 mm Hg were eligible. Cirrhosis was established by noninvasive and/or histological criteria. Compensated cirrhosis was defined by the absence of ascites, variceal hemorrhage, jaundice, or encephalopathy. Exclusion criteria were platelet count <50,000/mm^3, portal vein thrombosis, hypersensitivity to sildenafil, use of nitrates or BB, MAP <60 mm Hg, bacterial infection in the past 2 weeks,

Abbreviations used in this paper: BB, nonselective beta blockers; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; IQR, interquartile range; MAP, mean arterial pressure; NO, nitric oxide; PDEI, PDE-V inhibitor; PDE-V, phosphodiesterase-5; SBP, systolic blood pressure; WHVP, wedged hepatic venous pressure.

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Table 1. Percent of Change From Baseline at Each Time Point

Variables	Baseline (IQR), n = 12	Median % change at 30 minutes (range), n = 11	Median % change at 60 minutes (range), n = 12	Median % change at 90 minutes (range), n = 9	*P*
Systolic blood pressure	134 (124–149)	−6 (−16 to 0)[a]	−6 (−18 to 4)[a]	−8 (−12 to −16)[a]	.008
Diastolic blood pressure	70 (60–76)	−8 (−23 to 16)[a]	−5 (−40 to 9)[a]	−8 (−27 to 4)	.040
Mean arterial pressure	92 (84–95)	−8 (−16 to 13)[a]	−7 (−22 to 8)[a]	−9 (−17 to −2)[a]	.003
Heart rate	67 (60–73)	0 (−13 to 13)	+2 (−12 to 15)	+3 (−11 to 16)	.056
WHVP (*mm Hg*)	21.4 (18.0–27.0)	0 (−12 to 30)	+2 (−12 to 31)	−1 (−8 to 31)	.162
FHVP (*mm Hg*)	11.2 (8.5–13.3)	+1 (−28 to 16)	+4 (−32 to 38)	+11 (−21 to 53)	.007
HVPG (*mm Hg*)	10.4 (6.6–13.0)	+1 (−26 to 48)	−4 (−19 to 28)	−5 (−30 to 40)	.506

[a]Significantly different from baseline.

or active alcohol use in the past 6 months. The study was approved by the Ethics Committee of Yale and the Connecticut Veterans Affairs Healthcare System. All patients were studied at the Connecticut Veterans Affairs Health Care System and gave written informed consent.

Methods

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and MAP were obtained using Welch Allyn Propaq CS monitor (Model 242; Welch Allyn, New York, NY) every 5 minutes. Sedation was limited to ≤0.02 mg/kg of midazolam, a dose known to have no effect on the HVPG.[12,13] The HVPG was measured using the transjugular approach and a balloon-tipped catheter as previously described.[12] Measurements of free hepatic venous pressure (FHVP) and wedged hepatic venous pressure (WHVP) were obtained in triplicate. HVPG was calculated by subtracting the FHVP from the WHVP. Permanent electronic tracings were obtained using the PowerLab data acquisition system (ADInstruments, Inc., Colorado Springs, CO).

After baseline measurements, patients received an oral dose of 25 mg of sildenafil and measurements were repeated 30 and 60 minutes later. If the MAP had not decreased by >15% from baseline and the patient remained asymptomatic, a second dose of 25 mg of sildenafil was administered with measurements 30 minutes later, and the study was terminated. A dose of 50 mg of sildenafil was felt to be sufficient as it is the dose commonly used for erectile dysfunction.

Data Analysis

As this was a pilot proof-of-concept study, formal sample size calculations were not performed. Because a previous study[9] using the PDE-V inhibitor vardenafil demonstrated a median reduction in the HVPG in 5 patients of 16%, we assumed that investigating 10–12 patients would be sufficient to test whether this effect was reproducible and whether proceeding to a placebo-controlled trial would be warranted.

All HVPG tracings were read by 3 independent observers (I.I., G.G.-T., R.J.G.) who were blinded to the patient and sequence of tracings.

Baseline measurements of hemodynamic parameters were compared to 30, 60, and 90 minutes and expressed as percent (%) change from baseline. Statistical comparisons were made using the Friedman test. The Wilcoxon test was used to compare each time point to baseline if the Friedman result was significant. Statistical significance was considered a *P*-value of <.05. Statistical analysis was done using SPSS 14.0 (SPSS Inc, Chicago, IL). All results are expressed as medians ± interquartile ranges (IQRs), or as ranges for the percent changes in Table 1.

Results

Between September 2006 and March 2007, 18 patients were enrolled and had baseline hemodynamic measurements performed. Of these, 5 were excluded because of an HVPG <5 mm Hg and 1 because of software malfunction. All patients were male with a median age of 55 (IQR, 52–59) years. All patients were Child–Pugh class A with a median baseline albumin of 3.8 (IQR, 3.3–4.2) g/dL, bilirubin of 1.0 (IQR, 0.8–1.3) mg/dL, international normalized ratio of 1.2 (IQR, 1.0–1.4), and creatinine of 0.9 (IQR, 0.8–1) mg/dL. Cirrhosis was biopsy-proven in 11/12 patients and 58% had an alcoholic etiology. Baseline MAP was 92 (IQR, 84–95) mm Hg and baseline HVPG was 10.4 (IQR, 6.6–13.0) mm Hg.

Thirty-minute HVPG measurements were performed in 11 of 12 patients because the position of the hepatic vein catheter had to be readjusted in 1 patient. All patients had 60-minute measurements (expected peak effect of sildenafil). The 90-minute measurement was performed in only 9 patients.

Effect of Sildenafil on Systemic Hemodynamics

As shown in Table 1, SBP, diastolic blood pressure, and MAP (Figure 1) significantly decreased at all time points after sildenafil administration. None of the patients were symptomatic. The median decrease in MAP was 7 (IQR, 4.3–9.8) mm Hg at 30 minutes, 6.5 (IQR, 1.3–14.5) mm Hg at 60 minutes, and 8 (IQR, 2.3–11.8) mm Hg at 90 minutes. Heart rate did not change significantly (Table 1).

Effect of Sildenafil on Portal Hemodynamics

Compared with baseline, there were no significant changes in HVPG (Figure 1) or in WHVP. There was a statistically significant but mild and unexplained increase in FHVP.

Discussion

This proof-of concept study shows that the PDEI sildenafil does not reduce portal pressure in patients with compensated cirrhosis. In keeping with the widespread distribution of PDE-V,[6,14–17] although mild, the vasodilatory action of sildenafil