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Pharmacokinetics and Tolerability of Intravenous Sildenafil in Two Subjects with Child-Turcotte-Pugh Class C Cirrhosis and Renal Dysfunction

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Abstract

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Contributions

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Conflict of Interest

Robert H. Christenson, Ph.D. reported that he is a consultant for Roche Diagnostics and Siemens Healthcare Diagnostics and have research contracts with both.

Phosphodiesterase-5 (PDE-5) inhibitors have been used successfully in patients with cirrhosis to treat porto-pulmonary hypertension. Additionally, in cirrhosis, PDE-5 inhibitors can potentially improve portal hypertension and renal hemodynamics. No pharmacokinetics and tolerability studies of intravenous (IV) sildenafil have been conducted in Child-Turcotte-Pugh (CTP) class C cirrhosis and renal dysfunction. We report two subjects with CTP class C cirrhosis and estimated glomerular filtration rate of 25.8 and 22.4 ml/min/1.73m^2 treated with a single-dose, IV bolus injection of 2.5 mg sildenafil. Both subjects had diuretic-refractory ascites with model for end-stage liver disease scores of 25 and 35. Both subjects tolerated IV Sildenafil without side effects. The observed maximum concentrations of plasma sildenafil were 35 and 20.6 ng/ml, with modeled pharmacokinetic estimates for clearance (11.9 and 14.9 L/hr), volumes of distribution (72.8 and 77.3 L) and half-life (4.2 and 3.6 hrs). N-desmethyl sildenafil concentrations ranged from 3 to 40% of the parent concentrations. Our results showed that in CTP class C cirrhosis and renal dysfunction, IV bolus injection of 2.5 mg sildenafil is safe and tolerable.

Introduction

Phosphodiesterase-5 (PDE-5) inhibitors play an important role in the treatment of complications of cirrhosis. They have been used successfully to treat porto-pulmonary hypertension (PPHTN)[1–4], a complication in 5% of subjects with cirrhosis[5]. Additionally, previous studies showed that PDE-5 inhibitors reduced portal pressures and hepatic venous pressure gradients, thereby improving hemodynamics in cirrhosis[6–8]. Moreover, in cirrhotic rats, PDE-5 inhibitors increased fractional excretion of Na, reduced plasma renin levels, and improved renal blood flow and glomerular filtration rate[9].

In cirrhosis, diminished intrahepatic nitric oxide (NO) levels[6] are associated with elevated asymmetric dimethylarginine levels that inhibit NO synthesis by competing with L-arginine for nitric oxide synthase[10, 11]. In turn, reduced intrahepatic NO levels result in dysfunction of NO-activated guanylate cyclase and, consequently, reduced sinusoidal cyclic guanosine 3', 5' monophosphate (cGMP)[8]. cGMP depletion increases intrahepatic sinusoidal pressure[8], splanchnic vasodilation, activation of the renin-angiotensin-aldosterone system and development of renal vasoconstriction. PDE-5 inhibitors (e.g. sildenafil) block PDE-5 and increase cGMP levels, thereby also increasing intrahepatic and intrarenal NO bioavailability and thereby improves hemodynamics in cirrhosis[6–8].

Despite these encouraging findings, sildenafil is not approved by the Food and Drug Administration (FDA) for use in severe hepatic impairment[12] as no pharmacokinetic or safety data in subjects with CTP class C cirrhosis and renal dysfunction are available. To address this need, we treated two subjects with CTP class C cirrhosis and renal dysfunction (renal dysfunction defined as estimated glomerular filtration rate (eGFR) ≥ 15 and < 60 ml/min/1.73m^2 estimated by 6-variable Modification of Diet in Renal Disease (MDRD) equation[13]), with a single-dose, IV bolus injection of 2.5 mg sildenafil.

Methods

An Investigational New Drug (IND) application for sildenafil was filed with FDA and the study was approved by the Institutional Review Board of the University of Maryland,

Baltimore. Both subjects signed informed consent and were enrolled in the study. Patient 1 was a 59-year-old man with history of chronic hepatitis C cirrhosis admitted with worsening ascites, abdominal pain and acute kidney injury. Physical examination showed icteric sclerae, upper extremity muscle wasting, large ascites, splenomegaly and vascular spider on the upper anterior chest. He had a Model for End-Stage Liver Disease (MELD) score of 25. Prior to sildenafil administration, his aspartate aminotransferase (AST) level was 74 IU/L, alanine aminotransferase (ALT) 33 IU/L, alkaline phosphatase 111 IU/L, total bilirubin 2.7 mg/dL, albumin 4.1 g/dL, prothrombin time 19.8 sec and international normalized ratio (INR) 1.6. His eGFR was 25.8 ml/min/1.73 m^2. Patient 2 was a 46-year-old man with chronic hepatitis C and alcohol-induced cirrhosis who presented with elevated liver tests, jaundice, abdominal pain, and distention. Physical examination showed icteric sclerae, moderate ascites and generalized mild abdominal tenderness. He had a MELD score of 35. His AST level was 123 IU/L, ALT 48 IU/L, alkaline phosphatase 148 IU/L, total bilirubin 32.7 mg/dL, albumin 3.0 g/dL, prothrombin time 18.4 sec, INR 1.5. His eGFR was 22.4 ml/min/1.73 m^2. Both subjects denied hypersensitivity or allergy to sildenafil and its components.

After enrollment, subjects did not consume caffeinated and alcoholic beverages and avoided exercise or work activity outside their routine after enrollment. Subjects did not receive any non- selective beta-blockers, non-steroidal anti-inflammatory drugs, diuretics, midodrine, vasopressin, or octreotide within twenty-four hours prior to sildenafil administration and during the study. Additionally, IV fluids and albumin were stopped two hours prior to sildenafil administration. Both subjects fasted overnight and consumed 500 mL of water before sildenafil administration. All procedures were performed in the supine position. Before sildenafil injection, mean arterial blood pressure (MAP) was checked to ascertain that it was greater than 70 mmHg. MAP along with heart rate was also measured at 15, 30, 60, 120, 180, 240, 360 and 480 minutes after sildenafil administration. To eliminate factors that could interfere with the absorption phase (food, slow transit time, compliance issues), each patient received single-dose 2.5 mg of sildenafil by IV bolus injection. Plasma levels of sildenafil and its active metabolite N-desmethyl sildenafil levels were measured before and 15, 30, 60, 90, 120, 180, 240, 360 and 480 minutes after Sildenafil administration. Samples were centrifuged and stored at −80°C.

Plasma Sildenafil and N-Desmethyl-Sildenafil Measurements

Samples were assayed by Covance Laboratories, Inc (Madison, WI) using a validated method. Analyst® software (Version 1.5.1) was used to capture the (liquid chromatography-mass spectrophotometry/mass spectrophotometry (LC-MS/MS) data and integrate the peak areas. Watson LIMS software (Version 7.4.1) was used for data storage, management and reporting.

Pharmacokinetic Analysis

Plasma concentrations were analyzed by non-compartmental modeling using Phoenix® WinNonlin® version 5.1 (Certara L.P. (Pharsight), St. Louis, MO).

Results

Both subjects tolerated IV Sildenafil without side effects. No adverse events occurred up to 9 hours after sildenafil injection. Patient did not report any adverse events when they were interviewed forty-eight hours after sildenafil injection. Table 1 shows plasma sildenafil and N-desmethyl sildenafil concentrations before and after the administration of 2.5 mg IV Sildenafil with corresponding MAP and heart rate. The pharmacokinetic parameters of sildenafil and N-desmethyl-sildenafil are shown in Table 2. The modeled maximum concentrations were 34.4 and 32.3 ng/mL, clearance 11.9 and 14.9 L/hr, volumes of distribution 72.8 and 77.3 L and half-lives 4.2 and 3.6 hrs. N-desmethyl sildenafil concentrations ranged from 3 to 40% of the parent concentrations. For subject 1, the lowest MAP observed was 75 and occurred at 16 and 120 minutes after sildenafil injection. For subject 2, the lowest MAP was 69 mmHg and occurred at 15 minutes after sildenafil injection.

Discussion

We report two subjects with CTP class C cirrhosis and renal dysfunction who tolerated a single 2.5-mg IV injection of sildenafil without adverse events. Although prior studies reported the pharmacokinetics of sildenafil in subjects with CTP Class A and B cirrhosis, no data are available on subjects with CTP Class C cirrhosis[14]. In subjects with CTP class A and B cirrhosis, the mean clearance of sildenafil was reduced by 46% and Cmax was increased by 47% compared to normal controls after administration of a single 50 mg oral dose of sildenafil[14]. Additionally, the mean Cmax of N-desmethyl sildenafil, the active metabolite of sildenafil was increased by 87% compared to normal controls[14]. This increased systemic exposure in cirrhosis is likely explained by a combination of reduced hepatic clearance and reduced first-pass metabolism. We administered a single dose of 2.5 mg sildenafil by IV injection, thus eliminating the influence of first pass metabolism on systemic exposure.

As there is no pharmacokinetic study of IV sildenafil reported in the literature conducted in subjects with CTP class A or B cirrhosis, we compared the pharmacokinetic parameters of our two subjects with CTP class C cirrhosis to those obtained from healthy volunteers. The observed Cmax values of 34.4 and 32.3 ng/mL were slightly higher than the dose-corrected mean Cmax of 26.6 ng/mL reported in healthy volunteers[15]. Our observed clearance (CL) values of 11.9 and 14.9 L/hr were 63% and 71% lower than previous values of mean 40.8 L/hr in healthy volunteers[15]. The observed volumes of distribution (Vd) values of 72.8 and 77.3 L were markedly lower than the mean volume of 234 L reported in healthy volunteers[15]. The observed half-lives of 4.2 and 3.6 hrs were similar to the mean half-life of 3.9 hrs reported in healthy volunteers[15], and may be explained by the reduced clearance and volume of distribution.

Determination of N-desmethyl sildenafil, the active metabolite of sildenafil is important; in prior pharmacokinetic study of subjects with CTP Class A and B cirrhosis, N-desmethyl sildenafil Cmax and area-under-the-curve (AUC) increased by 87% and 154% compared to healthy subjects, respectively[14]. Elimination of active metabolite of sildenafil was more

impaired than sildenafil itself in subjects with CTP class A and B cirrhosis compared to healthy subjects; N-desmethyl sildenafil AUC/sildenafil AUC in subjects with CTP Class A and B cirrhosis was 71% whereas N-desmethyl sildenafil AUC/sildenafil AUC in healthy subjects was only 52%[14]. In our study, subject 1 had N-desmethyl sildenafil concentrations ranging from 3–40% of the parent concentrations. Subject 2 had unmeasurable metabolite concentrations except at 180 minutes after sildenafil injection, likely due to the lower parent drug concentrations resulting from the low dose (2.5 mg).

To our knowledge, this is the first report of pharmacokinetics and tolerability of IV sildenafil in subjects with CTP Class C cirrhosis and renal dysfunction. We conclude that sildenafil 2.5 mg injection can be safely administered in subjects with CTP Class C cirrhosis and renal impairment. The observed reductions in hepatic clearance and volume, coupled with reports of reduced first-pass effect, suggests that increased systemic exposure following oral dosing in subjects with CTP Class C cirrhosis would be predicted. Our findings indicate that studies of oral sildenafil in subjects with CTP class C and renal dysfunction to determine whether this benefits portal hemodynamics and renal function are safe and feasible.

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Table 1

Plasma Sildenafil and N-Desmethyl Sildenafil Concentrations in Two Subjects with CTP Class C Cirrhosis and Renal Dysfunction

Subject 1	Time after Sildenafil Injection (minutes)	Sildenafil Concentration (ng/mL)	N-desmethyl Sildenafil Concentration (ng/mL)	Mean Arterial Pressure (mmHg)*	Heart Rate*
1	Predose	BLQ	BLQ	87	50
1	16	35.0	1.21	75	53
1	30	25.7	BLQ	78	53
1	60	25.9	2.26	78	55
1	88	31.9	2.10	N/A	N/A
1	120	21.6	2.49	75	51
1	178	23.5	2.64	79	50
1	242	26.7	2.19	78	50
1	360	5.01	2.00	83	53
1	480	3.87	1.53	83	54
Subject 2	**Time after Sildenafil Injection (minutes)**	**Sildenafil Concentration (ng/mL)**	**N-desmethyl Sildenafil Concentration (ng/mL)**	**Mean Arterial Pressure (mmHg)***	**Heart Rate***
2	Predose	BLQ	BLQ	77	98
2	15	20.6	BLQ	69	98
2	30	16.0	BLQ	73	98
2	60	13.5	BLQ	75	98
2	90	12.0	BLQ	N/A	N/A
2	122	12.0	BLQ	81	90
2	180	10.2	1.06	80	97
2	240	9.79	BLQ	75	93
2	360	7.08	BLQ	72	92
2	480	8.02	BLQ	75	94

BLQ=Below llimit of quantitation

*At few time points, MAP and heart rate were measured 1 or 2 minutes earlier or later than plasma sildenafil and N-desmethyl sildenafil concentrations.

Table 2

Pharmacokinetics of Sildenafil and N-Desmethyl Sildenafil in Two Subjects with CTP Class C Cirrhosis and Renal Dysfunction

		Subject 1	Subject 2
Sildenafil			
	Vd (L)	72.8	77.3
	CL (L/hr)	11.9	14.9
	Half-life (hr)	4.2	3.6
	Cmax (ng/mL)	34.4	32.3
N-desmethyl Sildenafil			
	Cmax (ng/mL)	2.6	1.1