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DIALYSIS – TRANSPLANTATION

The pharmacokinetics and hemodynamics of sildenafil citrate in male hemodialysis patients

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The pharmacokinetics and hemodynamics of sildenafil citrate in male hemodialysis patients.

Background. Erectile dysfunction (ED) is highly prevalent in men with renal disease. The clearance of sildenafil citrate, a highly effective oral treatment for ED, is decreased in men with severe renal insufficiency, but the pharmacokinetic and hemodynamic profiles during maintenance hemodialysis in men with end-stage renal disease have not been studied.

Methods. Fifteen men undergoing chronic outpatient maintenance hemodialysis received a single 50-mg oral dose of sildenafil on 2 occasions, once 2 hours before, and once 2 hours after hemodialysis, with randomized assignment to sequence. Blood and dialysate samples were collected, and hemodynamic measurements were made.

Results. Hemodialysis did not significantly clear either sildenafil or its primary metabolite, UK-103,320. Administration after hemodialysis was associated with a 17% higher peak plasma concentration and earlier time to peak, which were not clinically meaningful, whereas the overall extent of absorption and the elimination half-life were not affected. The average extent of drug bound to plasma protein was approximately 96% in hemodialysis patients. Intradialytic hypotension was not observed more frequently when sildenafil was administered before hemodialysis. Systolic blood pressure tended to decrease less during hemodialysis when subjects were treated with sildenafil before dialysis.

Conclusion. The present study demonstrates that sildenafil is not cleared by hemodialysis, and the pharmacokinetic profile resembles more closely that observed in normal volunteers than that observed in patients with severe renal insufficiency. In addition, we found that sildenafil does not promote intradialytic hypotension.

Erectile dysfunction (ED) is a condition that is associated with cardiovascular diseases, including atherosclerosis, hypertension, and diabetes mellitus, and increasingly is recognized as being a consequence of vascular or endothelial dysfunction [1, 2]. The hemodialysis patient population has a high incidence of cardiovascular disease, and thus, it is not surprising that a majority of men receiving maintenance hemodialysis experience ED [3–6]. In a cross-sectional study of men from a community-based hemodialysis population, the prevalence of any degree of ED was 82%, and the prevalence of severe ED was 45% [4]. Furthermore, ED in hemodialysis patients has been shown to have a significant impact on quality of life measures [7]. Sildenafil citrate, introduced in 1998, is the first oral and most widely prescribed treatment for ED. Several studies have indicated that sildenafil is a well-tolerated and effective treatment for ED in men receiving maintenance hemodialysis [8–10]; however, the pharmacokinetic and hemodynamic profiles of sildenafil in this population, which are of interest from both clinical and pathogenetic perspectives, have not been systematically examined.

In healthy volunteers, sildenafil is extensively absorbed; however, rapid first-pass metabolism limits the absolute bioavailability to approximately 40%, C_{max} is reached within 30 to 120 minutes of oral administration in the fasted state, and the terminal half-life is about 4 hours [11]. Sildenafil is converted to a number of metabolites by the hepatic P450 enzymes CYP3A4 and CYP2C9. The primary *N*-demethylated product, UK-103,320, has a slightly longer half-life, approximately half the pharmacologic activity, and achieves approximately 40% of the plasma concentration of the parent compound, resulting in approximately 14% of the total pharmacologic effect of the drug [12, 13]. Both sildenafil and UK-103,320 are more than 95% bound to plasma proteins, independent of total drug concentrations [14]. Sildenafil is eliminated by hepatic metabolism and excreted as metabolites predominantly in the feces (approximately 80% of an oral dose), with only a small amount excreted in the urine (approximately 13% of an oral dose) [13]. In men with mild or moderate renal impairment, the pharmacokinetics were not significantly different

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from those in normal men [12]. However, in patients with severe renal insufficiency (creatinine clearance <30 mL/min), the clearance of sildenafil is reduced by half, resulting in an increased bioavailability [approximately doubled area under the curve (AUC) and maximum concentration of the drug (C_{max})] compared with healthy normal volunteers [12].

Sildenafil acts through the nitric oxide-cGMP pathway [15, 16], and enhanced nitric oxide (NO) biosynthesis has been correlated with blood pressure decreases observed during hemodialysis [17–21]. Previous studies did not indicate adverse hemodynamic effects of sildenafil during hemodialysis, but these studies did not systematically evaluate blood pressure, nor did they control for the timing of sildenafil administration with respect to hemodialysis therapy. Because sildenafil inhibits the breakdown of NO-stimulated cyclic GMP [22], hemodialysis-associated blood pressure changes observed in patients administered sildenafil should help test the hypothesis that NO plays a role in the hemodynamic regulation during hemodialysis.

Therefore, this study was designed to assess the pharmacokinetics of a 50-mg dose of sildenafil in subjects with end-stage renal disease (ESRD) (primary objective), and to test the maximal hemodynamic effect by administering sildenafil 2 hours before, and 2 hours after, hemodialysis.

METHODS

Subjects

Sixteen male subjects older than 18 years of age receiving routine outpatient hemodialysis therapy 3 times weekly for at least 3 months, and having a hematocrit greater than or equal to 32%, were recruited for participation in this study. Subjects had to have a functioning hemodialysis fistula, either native vein fistula or a gortex graft, for use during the hemodialysis treatments. Men who were taking nitrates or NO donors (e.g., nitroglycerin or isosorbide dinitrate) in any form (oral, sublingual, transdermal, inhalation, or aerosols) were specifically excluded from the study. Use of protease inhibitors or the non-nucleoside reverse transcriptase inhibitor delavirdine were also prohibited because they inhibit the sildenafil metabolizing cytochrome P450 enzyme 3A4. Other exclusion criteria were a resting systolic blood pressure (SBP) of >180 or <90 mm Hg, or a resting sitting diastolic blood pressure (DBP) of >110 or <50 mm Hg, >40% of their weight range for age, gender, height, and frame, as established in the 1996 Metropolitan Life Insurance Height and Weight Tables [23], report of hypotension during more than 3 hemodialysis treatments out of the previous 36 treatments, a known history of retinitis pigmentosa, a history of hypersensitivity reaction to the dialysis membrane (polysulfone), and a known history of hypersensitivity or previous intolerance to sildenafil or any of the other tablet components. All subjects provided informed written consent before study entry. The protocol was approval by the local Institutional Review Board before study initiation.

Treatments

All subjects received treatment with a single 50-mg oral dose of sildenafil citrate (Viagra®; Pfizer, Inc., New York, NY, USA) at each of 2 dosing phases, separated by an interval of approximately 1 week. Hemodialysis treatments were 3.5 hours in duration and used an F80A dialyzer (Fresenius Medical Care, Lexington, MA, USA). Procedures were fixed for all patients through both phases. Appropriate blood flow rate was determined by the investigator, and every effort was made to maintain the flow at a constant flow rate above 300 mL/min throughout the dialysis period. Needles used were 15-gauge, and the dialysate flow rate was fixed at 500 mL/min. Dialysate was bicarbonate-based and contained Na 140 mEq/L, and K, HCO_3, and Ca as appropriate. In phase A, hemodialysis was started 2 hours after dosing with sildenafil, and ended 5.5 hours after dosing. In phase B, hemodialysis began 5.5 hours before dosing with sildenafil, and ended 2 hours before dosing (Fig. 1).

Study design

The study followed a randomized, 2-phase crossover, open-label design, and was conducted at a single site (Total Renal Research, Hennepin County Medical Center, Minneapolis, MN, USA). There were a total of 3 study visits. Subjects were screened no more than 2 weeks before the first dosing phase. At each of 2 dosing visits, subjects were under observation through 48 and 42 hours postdose for phases A and B, respectively. Subjects were randomized to phase order (sequence). In phase A, patients received sildenafil 2 hours before the start of hemodialysis; in phase B, the same treatment was administered 2 hours after the completion of hemodialysis (Fig. 1). Blood and dialysate samples were collected for analysis of sildenafil and UK-103,320 concentrations, and hemodynamic measurements of blood pressure and heart rate were performed at prespecified time points through 48 hours' postdose in phase A, and 42 hours' postdose in phase B.

Pharmacokinetic sampling

Venous blood samples were collected for sildenafil and UK-103,320 assays immediately before sildenafil dosing, at 30-minute intervals through 6 hours' postdosing (except for 1.5 hours' postdosing), and at 7, 8, 10, 12, 18, and 24 hours' postdosing during both dosing phases. End-of-phase venous blood samples were collected at 48 hours' postdose in phase A and at 42 hours' postdose in phase

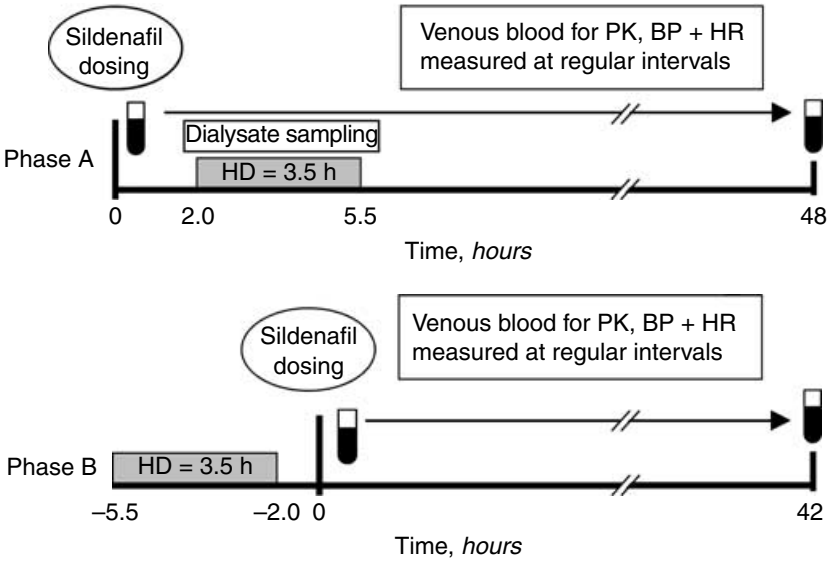

Fig. 1. Study design. In phase A, subjects received a single oral dose of sildenafil (50 mg) at time 0, 2 hours before the start of hemodialysis (HD), which lasted 3.5 hours. In phase A, inlet (arterial), outlet (venous), and dialysate samples were collected for pharmacokinetic (PK) determinations. In phase B, subjects received a single oral dose of sildenafil (50 mg) at time 0, 2 hours after the completion of HD. In both phase A and phase B, venous blood was drawn at regular intervals after sildenafil administration for PK determinations. Blood pressure (BP) and heart rate (HR) were measured at regular intervals for the duration of both phases.

B. During dialysis in phase A, samples were collected every 30 minutes simultaneously at the inlet (arterial) and outlet (venous) sides of the dialyzer, as well as from the dialysate.

Analytical methods

All plasma and dialysate samples were assayed for sildenafil and UK-103,320 with a previously validated method, which employed automatic sample preparation using an automated sequential trace enrichment of dialysates (ASTED) method, and separation of the analytes by reversed phase high-pressure liquid chromatography with subsequent ultraviolet detection [24]. The lower limit of quantification for all analyses was 1.00 ng/mL. The calibration curves for both analytes were linear over the range of 1 to 250 ng/mL. The overall imprecision (coefficient of variation) was 5.1%, 3.2%, and 3.0% for sildenafil and 3.4%, 3.1%, and 2.9% for UK-103,320 concentrations of 3.00, 125, and 200 ng/mL, respectively. The inaccuracy (bias) of the assay at all concentrations ranged from −2.3% to 3.5% for sildenafil and −7.0% to 4.8% for UK-103,320. Protein binding was determined by equilibrium dialysis.

Hemodynamic measurements

Blood pressure and heart rate measurements were performed immediately before sildenafil dosing, at 30-minute intervals through 6 hours' postdosing (except at 1.5 hours), and at 7, 8, 10, 12, 18, and 24 hours postdosing throughout both dosing phases. In addition, in phase B, blood pressure and heart rate were measured at 30-minute intervals during hemodialysis, and 1 hour after hemodialysis, before sildenafil dosing.

Data analysis

The following pharmacokinetic parameters were calculated: C_{max}, T_{max} (time from dosing to the first occurrence of C_{max}), k_D (terminal elimination phase rate constant), AUC (total area under the plasma concentration vs. time curve from time zero to infinity), $t_{1/2}$ (terminal elimination half-life), CL_d (drug clearance due to dialysis), and R_h (drug removal due to dialysis).

CL_d was calculated using the formula: $CL_d = Q_d \times AUC_{(dia)}/AUC_{(art)}$, where Q_d is the rate of dialysate flow, $AUC_{(dia)}$ is the area under the dialysate concentration versus time curve, and $AUC_{(art)}$ is the area under the arterial plasma concentration versus time curve during dialysis (see equation 13 of Lee and Marbury [25]). R_h was calculated using the formula: $R_h = CL_d \times AUC_{(art)}$ (see equation 30 of Lee and Marbury [25]).

The log-transformed values of C_{max} and AUC and the untransformed values of $t_{1/2}$ and T_{max} were analyzed using the analysis of variance (ANOVA), including fixed effects of sequence (AB or BA), subject within sequence, period (visit 2 or visit 3), and dosing phase (A or B). The residual variance of this analysis was used to construct 90% 2-sided CIs on the ratio of the geometric means of phase B to phase A (after hemodialysis dosing/before hemodialysis dosing) for C_{max} and AUC. A 90% 2-sided CI was also constructed for the difference between dosing phases in T_{max} and $t_{1/2}$. These analyses were performed separately for sildenafil and UK-103,320.

Systolic and diastolic blood pressures and heart rates were analyzed through 10 hours after the start of hemodialysis using repeated measures analysis of variance (ANOVA) of the changes from baseline values, where baseline was the time point just before the start of hemodialysis in each dosing phase. Separate analyses of intradialytic and postdialysis blood pressures were

Table 1. Demographics

Characteristic	$N = 16$
Mean age, *years* (range)	48 (33–75)
Mean weight, *kg* (range)	75 (51–107)
Mean duration of end-stage renal disease, *years* (range)	8 (0.4–22)
Smoking history, *N*	
Smoker	9
Never smoked	6
Past smoker	1
Race, *N*	
Black	12
White	3
Hispanic	1
Primary cause end-stage renal disease, *N*	
Glomerulonephritis	7
Hypertension	4
Diabetes	3
NSAID-induced	1
Unknown	1
Comorbid diseases, *N*	
Anemia	16
Hypertension, essential unspecified	16
Kidney/ureter disorder	15
Phosphorus metabolism disorder	14
Rheumatism	12
Hyperparathyroidism	11
Pruritic disorder, unspecified	5
Hypercholesterolemia	5
Diabetes mellitus	4
Hypotension, essential unspecified	4
Esophagitis	4

performed. In phase B, the data collected at 4.5 hours and 5.5 hours after the start of hemodialysis (–1 hour and 0 hour, relative to dosing time) were assigned to 4 hours and 5 hours postbaseline, respectively, to permit comparison by time point with the phase A data. The unadjusted blood pressures and heart rates were analyzed similarly.

Hypotension was defined as (*1*) >40 mm Hg decrease in SBP during hemodialysis, (*2*) SBP <90 mm Hg, (*3*) DBP <40 mm Hg, or (*4*) any clinical symptoms of decreased blood pressure.

RESULTS

Subject enrollment and disposition

The 16 subjects ranged in age from 33 to 75 years (mean 47.6 ± 12.1), and had been diagnosed with ESRD for 0.4 to 21.8 years (mean 8.2 ± 6.8; Table 1). Medical histories (Table 1) and concomitant medication use were consistent with the diagnosis of renal failure and its complications: 100% were taking anticoagulants and drugs used to treat anemia, 94% were taking antihypertensive drugs, 94% were taking calcium replacement, 69% were taking electrolyte replacements, 50% were taking analgesics, 12.5% were taking drugs for hyperlipidemia, and 12.5% were taking oral antidiabetic drugs. All subjects had active histories of anemia and essential hypertension. One subject discontinued at the end of the first dosing visit (phase A) because of noncompliance with study procedures. He was not included in the pharmacokinetic or hemodynamic analyses.

Table 2. Sildenafil and UK-103,320 pharmacokinetic parameters after a single 50-mg dose of sildenafil administered either before or after hemodialysis

	Phase A (mean ± SD)	Phase B (mean ± SD)	Ratio of geometric means (B/A)[a] [95% CI]
Sildenafil			
AUC *ng·h/mL*	610 ± 491	564 ± 455	
Geometric mean	474	466	98% [84–116]
C_{max} *ng/mL*	139 ± 82	164 ± 121	
Geometric mean	117	136	117% [92–148]
T_{max} *hours*	2.10 ± 1.06	1.43 ± 0.94	–1.20 to –0.19[b]
$t_{1/2}$ *hours*	3.07 ± 0.99	3.38 ± 1.18	–0.27 to –0.81
CL_d *mL/min*	8.7 ± 7.4	–	–
R_h *mg*	0.13 ± 0.14	–	–
UK-103,320			
AUC *ng·h/mL*	635 ± 420	582 ± 350	
Geometric mean	492	47	96% [84–111]
C_{max} *ng/mL*	105 ± 60	124 ± 75	
Geometric mean	88	107	122% [105–141]
T_{max} *hours*	2.53 ± 1.87	1.53 ± 0.93	–1.84 to –0.07
$t_{1/2}$ *hours*	4.86 ± 2.01	6.31 ± 2.28	0.79 to 2.09[c]
CL_d *mL/min*	22.2 ± 9.1	–	–
R_h *mg*	0.22 ± 0.16	–	–

[a] Phase A, sildenafil administered 2 hours before hemodialysis; phase B, sildenafil administered 2 hours after hemodialysis. For T_{max}, and $t_{1/2}$, the confidence intervals shown are for the differences (B–A) of the adjusted arithmetic means from the analysis of variance.
[b] $P < 0.05$.
[c] $P < 0.01$.

Pharmacokinetics

The average extent of administered drug bound to plasma proteins was 95.6% in phase A and 96.3% in phase B. Drug clearance caused by dialysis was minimal (CL_d; Table 2). Both sildenafil and UK-103,320 were essentially undialyzed, with less than 1% of the administered dose recovered in the dialysate (R_h; Table 2).

Mean plasma concentrations of sildenafil were similar whether sildenafil was administered 2 hours before the start of hemodialysis (phase A) or 2 hours after the end of hemodialysis (phase B) (Fig. 2). The rate of absorption of sildenafil appeared to be somewhat faster when drug was administered 2 hours after hemodialysis, as indicated by differences in T_{max} and C_{max} (Table 2). The extent of absorption, however, was unaffected by hemodialysis, as shown by the ratio of geometric means of AUC. The sildenafil terminal half-life, $t_{1/2}$, appeared to be similar with both dosing schemes.

In general, the trends seen for sildenafil between the 2 dosing schemes were also evident for UK-103,320. However, the mean $t_{1/2}$ of the metabolite was shorter when sildenafil was administered 2 hours before hemodialysis compared with 2 hours after hemodialysis (Fig. 2). Statistical analysis showed no significant effects of sequence ($P \geq 0.25$ for all parameters) or period (visit 2 or visit 3;

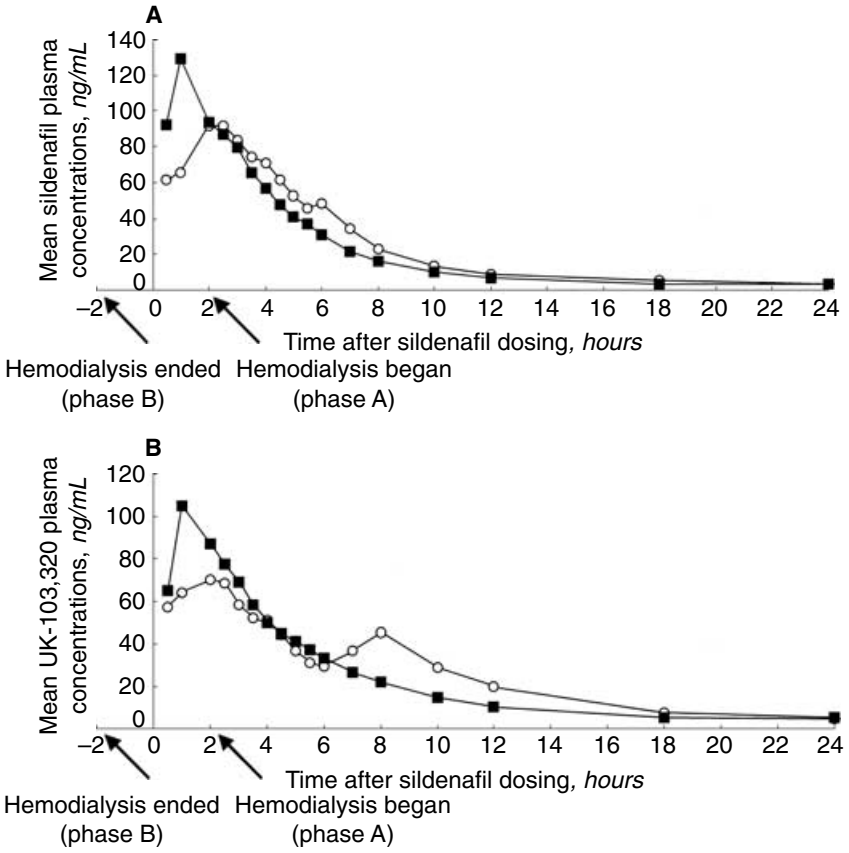

Fig. 2. Plasma drug concentrations. Mean sildenafil (*A*) and its metabolite, UK-103,320 (*B*), plasma concentrations were not significantly different after a single 50-mg dose of sildenafil administered 2 hours before (○, phase A) or 2 hours after (■, phase B) hemodialysis.

$P \geq 0.22$ for all parameters) for either sildenafil or UK-103,320.

Hemodynamics

In phase A, mean blood pressure at dosing was 142/85 mm Hg, and decreased to 132/77 mm Hg before the initiation of hemodialysis 2 hours later (Table 3). This response is consistent with the blood pressure decrease observed in normal volunteers [26]. During hemodialysis, SBP decreased 5.6 ± 10.4 mm Hg at 30 minutes, and remained at approximately that level until the conclusion of hemodialysis (Fig. 3, Table 3). DBP during phase A hemodialysis was variable and followed no discernible pattern, but decreased on average no more than 7 mm Hg (Fig. 3).

In phase B, mean blood pressure at the initiation of hemodialysis was 151/85 mm Hg (Table 3). SBP decreased 5.8 ± 15.5 mm Hg from baseline (initiation of hemodialysis) at 30 minutes, and then for the duration of dialysis decreased to a level 11 to 15 mm Hg lower than baseline (Fig. 3, Table 3). Diastolic blood pressure decreased on average no more than 8 mm Hg, and followed no discernible pattern (Fig. 3). No statistically significant differences in intradialytic SBP, DBP, or heart rate (Fig. 3, Table 3) were observed between phases A and B. It is important to note that predialysis weight and intradialytic weight change were similar for hemodialysis treatments in the 2 phases. Predialysis weights were 75.4 kg and 75.5 kg, and mean intradialytic weight changes were −2.8 kg and –2.7 kg, for phases A and B, respectively.

Intradialytic hypotension was predefined by accepted criteria (see **Methods**). Eight subjects who participated in both phases of the study experienced hypotension by the predefined criteria: 4 subjects in phase A, and 4 different subjects in phase B. Of these, only 1 subject in each phase

Table 3. Blood pressure in men administered sildenafil either 2 hours before or 2 hours after hemodialysis

Study event, time after dosing	Blood pressure, mean ± SD *mm Hg* Systolic	Diastolic
Phase A: dosing 2 hours before hemodialysis		
Sildenafil administration (time 0)[a]	142 ± 18	85 ± 12
Hemodialysis start (+2.0 h)[b]	132 ± 20	77 ± 12
Hemodialysis end (+5.5 h)	129 ± 23	71 ± 16
10 hours after hemodialysis start (+12.0 h)	126 ± 15	71 ± 11
Phase B: dosing 2 hours after hemodialysis		
Hemodialysis start (−5.5 h)[b]	151 ± 18	85 ± 12
Hemodialysis end (−2.0 h)	139 ± 22	81 ± 13
Sildenafil administration (time 0)[a]	131 ± 21	79 ± 14
10 hours after hemodialysis start (+4.5 h)	131 ± 23	79 ± 16

[a]Time 0 was defined as the time at which sildenafil was administered. In phase B, administration occurred 5.5 hours after the start of hemodialysis.
[b]The time at which hemodialysis started was used as baseline for statistical analysis of hemodynamic results.

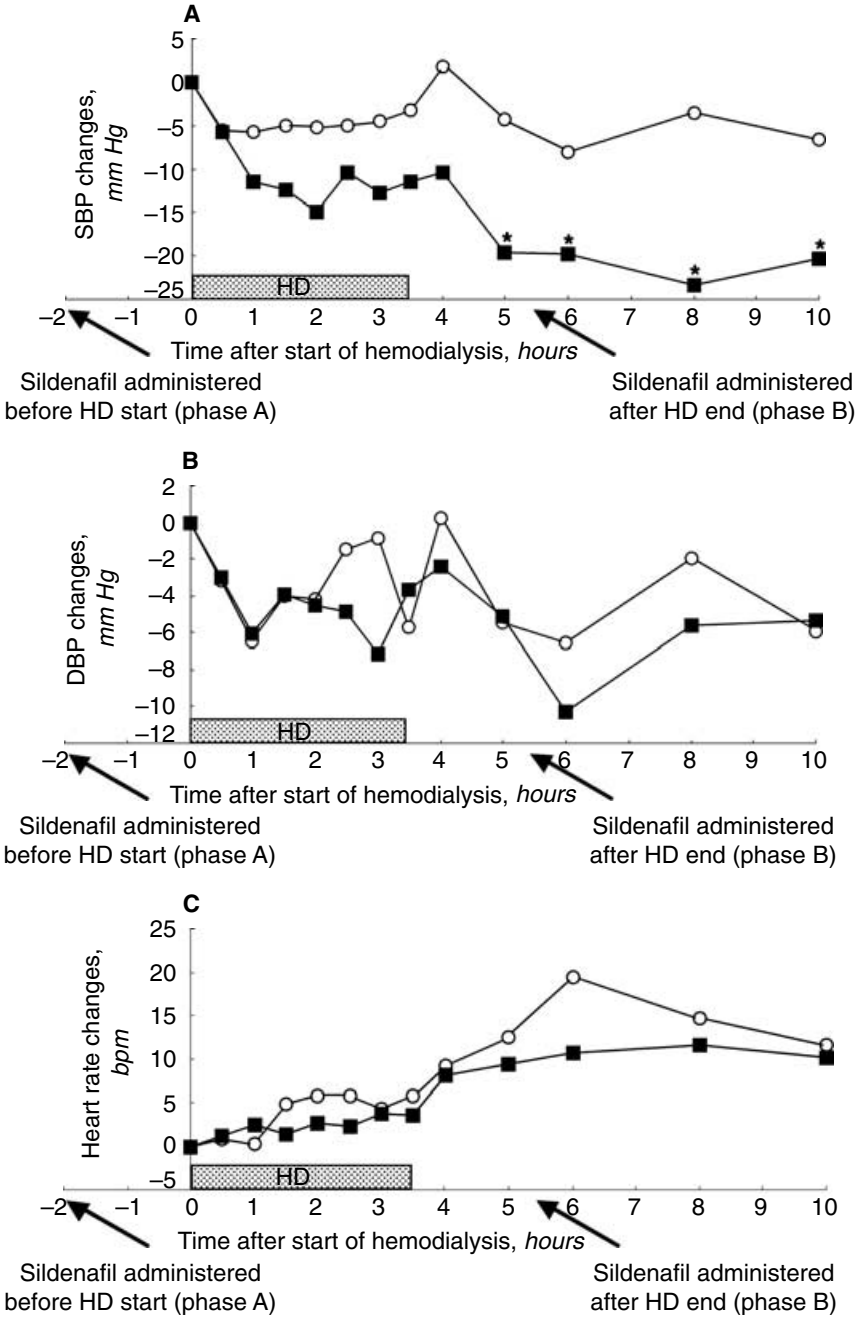

Fig. 3. Hemodynamic changes. Systolic blood pressure (SBP) changes (*A*) were significantly different between phase A (sildenafil administration 2 hours before hemodialysis (HD); ○) and phase B (sildenafil administration 2 hours after HD; ■) in the post-HD period (*$P < 0.05$). Diastolic blood pressure (DBP) changes (*B*) from the start of HD were not significantly different between phase A (○) and phase B (■). There were no significant changes in heart rate during phase A (○) or phase B (■) (*C*).

experienced symptoms of hypotension in the absence of a documented decrease in blood pressure.

After hemodialysis, SBP in phase A initially returned close to the baseline value, and manifested a mean decrease from baseline of 4.2 mm Hg for the 6 hours after dialysis (Fig. 3). In contrast, SBP in phase B manifested a decrease of 19.7 mm Hg from the baseline value after the conclusion of hemodialysis and before sildenafil dosing (Fig. 3), and the mean decrease for the 6 hours after dialysis was 18.7 mm Hg ($P < 0.05$ vs. phase A). DBP behavior following hemodialysis followed no clear pattern in either phase A or B, and no statistically significant differences were seen (Fig. 3). Heart rate showed a trend upward in the postdialysis period in both phases (Fig. 3).

Adverse events

Twelve subjects experienced a total of 41 treatment-emergent adverse events, which were evenly distributed between the 2 phases of the study, and the events were

expected in the population of hemodialysis patients. No subject discontinued because of adverse events. There was one serious adverse event (hospitalization for right hip pain caused by degenerative joint disease and right hip effusion) that occurred more than 2 weeks after dosing and was not related to treatment. No adverse events were severe. The most commonly reported treatment-emergent adverse events were asthenia ($N = 5$), fever ($N = 4$), and dizziness ($N = 3$); of these, only fever was considered to be related or possibly related to treatment. All other adverse events occurred 2 or fewer times. Two episodes of syncope were experienced by 2 different subjects; neither of these was accompanied by a documented decrease in blood pressure: both were of a "momentary" or "transient" nature, lasting seconds, and 1 accompanied signs, symptoms, and laboratory evidence of systemic infection (fever, chills, and positive blood cultures).

DISCUSSION

This study demonstrates that hemodialysis does not clear sildenafil or its major metabolite UK-103,320, which are both highly protein-bound. The rate of sildenafil absorption may be more rapid when hemodialysis precedes dosing, but the observed differences are not clinically meaningful. Interestingly, the pharmacokinetic profiles of sildenafil and UK-103,320 are closer to those observed in healthy volunteers [17] than those measured in subjects with severe renal insufficiency [12].

A possible explanation for why sildenafil pharmacokinetics can become altered in patients with severe renal insufficiency may be related to the effects of endogenous inhibitors of sildenafil metabolism that accumulate in the absence of normal renal function. A similar circumstance has been observed for the nonselective β-adrenoceptor antagonist bopindolol [27]. As is the case for sildenafil, bopindolol accumulates in patients with chronic renal insufficiency, but its disposition in patients receiving routine maintenance hemodialysis does not differ significantly from that in patients with normal renal function [27]. Hence, hemodialysis may remove the endogenous inhibitors of metabolism of bopindolol and sildenafil, and thereby restore the pharmacokinetics closer to that observed in patients with normal renal function.

Intradialytic hypotension was observed with the same frequency in this study whether the subject took sildenafil before hemodialysis or after hemodialysis, and the rates of hypotension observed were similar to those cited in the literature of approximately 20% to 30% [28, 29]. SBP decreased on average 5 to 6 mm Hg in the first 30 minutes of hemodialysis therapy, whether or not sildenafil was present, but subsequently, intradialytic SBP showed a trend toward greater lowering in the absence of sildenafil exposure. No effect or trend could be discerned for intradialytic DBP or heart rate.

During the 6-hour period after hemodialysis therapy, SBP was significantly lower when sildenafil was administered 2 hours after dialysis had ended, but the majority of this observed decrease occurred before dosing. DBP behavior in the 2 phases of the study was similar but without a clear pattern, and heart rate tended to increase postdialysis in both phases of the study.

The hemodynamic observations in this study indicate that sildenafil does not increase the rate of hypotension or cause concerning blood pressure changes, and these observations are consistent with those in the literature. In previous reports, patients on maintenance hemodialysis have tolerated sildenafil treatment well [8–10], with only one case report of a hemodialysis patient experiencing symptoms, including lightheadedness and dizziness after a 50-mg dose of sildenafil on an interdialytic day, and blood pressure was 80/50 the following day [30]. Nonetheless, the same prudent considerations should be applied to sildenafil as for the administration of any vasodilator in the presence of intravascular volume depletion, which may occur during and after hemodialysis therapy.

These hemodynamic observations may bring the role of NO in the pathogenesis of intradialytic hypotension [31] into question. Sildenafil inhibits phosphodiesterase 5, which is responsible for the breakdown of cGMP, the mediator of the vasodilating effect of NO. If NO were to be an important component in the genesis of hypotension during hemodialysis, an increase in cGMP-mediated vascular smooth muscle would be expected to be the pathogenetic mechanism, and sildenafil would be expected to potentiate the effect of NO by inhibiting the degradation of cGMP. Yet neither an increased incidence of hypotension, nor the behavior of intradialytic blood pressure in the presence of sildenafil in this study, supports this hypothesis. However, given the limited and selected nature of the patient population, further confirmation of these findings will be necessary.

CONCLUSION

The present study demonstrated that sildenafil was not cleared by hemodialysis, that there were no clinically significant differences in the pharmacokinetic profiles of sildenafil when administered either 2 hours before or after hemodialysis, and that the pharmacokinetic profiles resembled more closely those observed in normal volunteers than those observed in patients with severe renal insufficiency. Intradialytic hypotension was not observed more frequently when sildenafil was administered before hemodialysis, and the behavior of blood pressure in this study did not support an important role for NO in the pathogenesis of intradialytic hypotension.

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