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Acute Hemodynamic Effects of Single-Dose Sildenafil When Added to Established Bosentan Therapy in Patients With Pulmonary Arterial Hypertension: Results of the COMPASS-1 Study

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T*his study investigated the acute pharmacodynamic effects of sildenafil in patients with pulmonary arterial hypertension (PAH) and concomitant bosentan treatment, in view of a mutual pharmacokinetic interaction between the 2 drugs. This prospective, open-label, noncomparative, multicenter, phase II study enrolled 45 patients (≥18 years) with stable PAH (idiopathic, familial, or related to corrected congenital systemic-to-pulmonary shunts, drugs, or toxins) and on bosentan treatment for at least 3 months. Patients underwent right heart catheterization to evaluate the acute hemodynamic effects of (a) inhaled nitric oxide (iNO) and (b) a single oral dose of sildenafil (25 mg). Mean pulmonary vascular resistance (PVR) decreased from baseline following iNO (–15%; 95% confidence limits: –21%, –8%;* P = .0001*). A statistically significant decrease from baseline in mean PVR was also observed 60 minutes following sildenafil administration (–15%; 95% confidence limits: –21%, –10%;* P < .0001*). The reduction in PVR following sildenafil was comparable to that resulting from iNO. There were no unexpected safety findings. The pharmacodynamic effect suggests that addition of sildenafil to bosentan treatment can elicit additional hemodynamic benefits. These data represent a rationale for long-term combination studies with the 2 compounds.*

Keywords: *Pulmonary arterial hypertension; bosentan; sildenafil; pharmacodynamics*

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Pulmonary arterial hypertension (PAH) is a devastating, life-threatening disease with a rapid progression and poor prognosis when untreated.[1] It is characterized by a progressive elevation of pulmonary arterial pressure and pulmonary vascular resistance (PVR) and can eventually result in right heart failure and death.

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Among the many signaling pathways that are involved in the development of PAH, only 3 have so far been translated into approved therapies. The endothelin-mediated, the nitric oxide–mediated, and the prostacyclin-mediated pathways[2,3] have been targeted using endothelin receptor antagonists, phosphodiesterase type 5 (PDE-5) inhibitors, and prostacyclin/prostacyclin analogs, respectively (see Figure 1). The targeting of a single pathophysiological pathway may be insufficient to relieve symptoms in all patients, and the simultaneous targeting of multiple pathways may represent a viable alternative therapeutic strategy.[4] Therefore, combination of bosentan, an oral dual endothelin receptor antagonist, and sildenafil, an oral PDE-5 inhibitor, is expected to have additive or synergistic therapeutic effects in PAH, as each treatment acts on a different signaling pathway.

The approved dosing regimen for bosentan treatment of PAH in adults weighing >40 kg is 62.5 mg

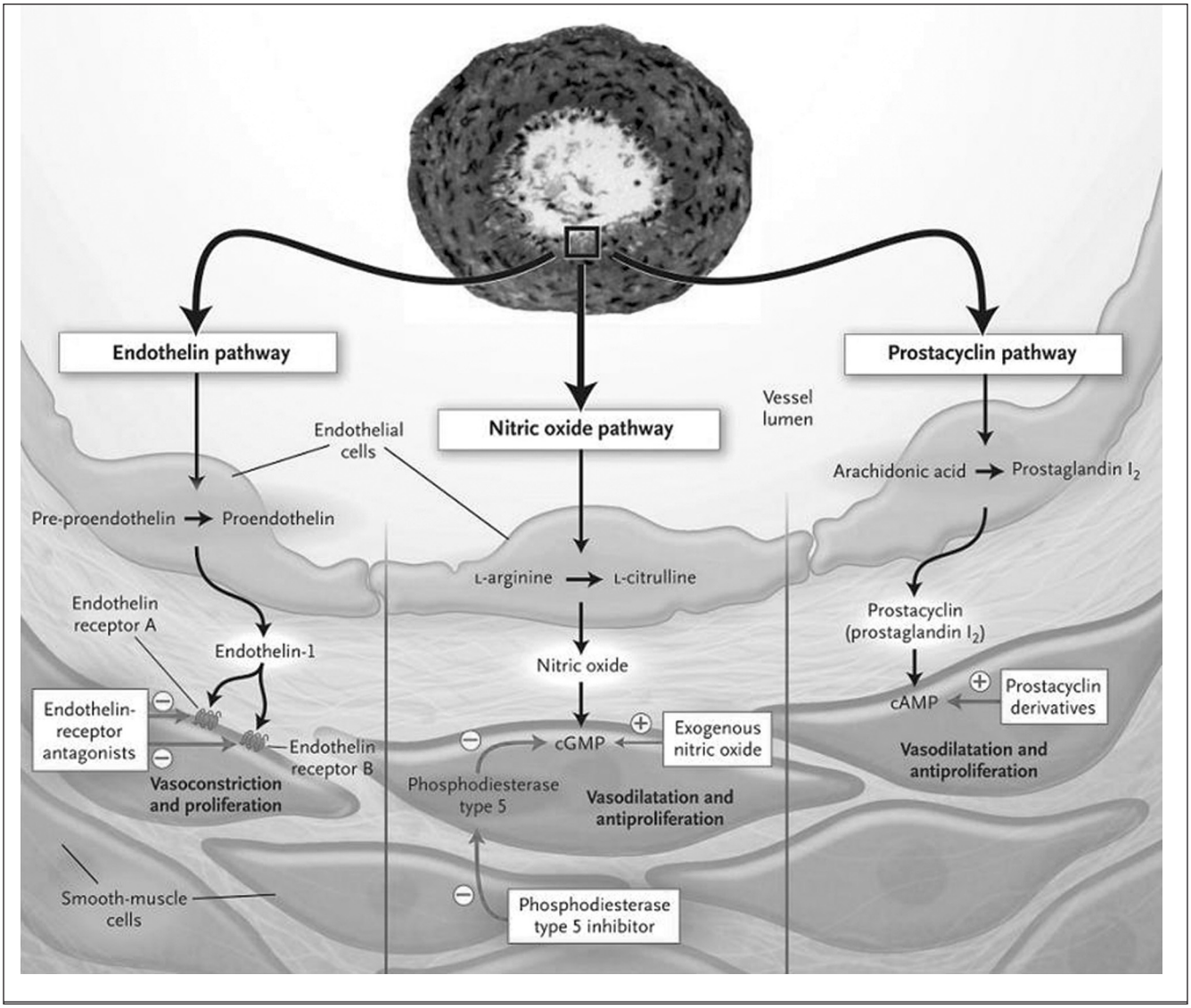

Figure 1. The 3 pathways targeted by pulmonary arterial hypertension (PAH) therapies . From Humbert et al,[3] reprinted with permission from the Massachusetts Medical Society. cGMP, cyclic guanidine monophosphate; cAMP, cyclic adenosine monophosphate.

bid initially, uptitrated to 125 mg bid after 4 weeks. After oral administration, maximum plasma concentrations of bosentan are attained within 3 to 5 hours, and the terminal elimination half-life ($t_{1/2}$) is about 5 hours in healthy adults, with a C_{max} of approximately 1000 ng/mL. The absolute bioavailability of bosentan in normal volunteers is about 50% and is unaffected by food. Exposure to bosentan increases proportionately for doses of 3 to 600 mg. Protein binding is approximately 97%, almost entirely to albumin.[5]

The approved sildenafil dosing regimen for the treatment of PAH is 20 mg tid. Maximum plasma concentrations at this dose are reached by approximately 1 hour after oral administration, and the $t_{1/2}$ is approximately 4 hours in healthy adults, with a C_{max} of 145 ng/mL. Absolute bioavailability is approximately 40%, which is reduced by 11% after a heavy meal.[6] Exposure to sildenafil is also proportionate to dose. It is predominantly metabolized to the active metabolite, N-desmethylsildenafil, which has the same PDE-5 specificity and half the potency of the parent drug. Protein binding for sildenafil and its metabolite is approximately 97%.[7] Therefore, clinical studies evaluating sildenafil

assess the combined hemodynamic effects of both substances.

Preclinical data on the combination of bosentan with sildenafil have shown synergistic effects on hemodynamics and survival in a rat model of monocrotaline-induced pulmonary hypertension.[8] Preliminary clinical data suggest that the combination of bosentan with sildenafil is well tolerated and may be beneficial for the treatment of PAH.[9-12]

However, there is evidence of a mutual pharmacokinetic interaction between bosentan and sildenafil, which may influence the pharmacodynamics of each drug in a combination treatment regimen. Coadministration of 125 mg bid bosentan and 80 mg tid sildenafil to healthy volunteers has been found to decrease C_{max} and AUC_{τ} (area under the curve over a dosing interval) of sildenafil by 55% (95% confidence limits [CL]: 40%-67%) and 63% (95% CL: 57%-68%), respectively, whereas sildenafil increased bosentan C_{max} and AUC_{τ} by 42% (95% CL: 15%-75%) and 50% (95% CL: 29%-75%), respectively.[13] This reduction in sildenafil exposure is caused by bosentan, which is known to induce expression of cytochrome P450 isozymes CYP2C9 and CYP3A4,[14] both of which are involved in the metabolism of sildenafil.[15] Sildenafil may increase the exposure to bosentan by inhibition of hepatic uptake via human organic anion-transporting polypeptides OATP1B1 and OATP1B3.[16] When coadministered to PAH patients, bosentan (125 mg bid) was shown to decrease sildenafil (100 mg, single dose) C_{max} and plasma half-life ($t_{1/2}$) by 56% and 37%, respectively.[17] As a consequence, the coadministration of bosentan with the sildenafil dosing regimen currently approved for PAH (20 mg tid) may result in exposure to sildenafil lower than that investigated in controlled clinical trials and potentially diminish its therapeutic effect.

As the current focus in the management of PAH is on the use of combination therapies, any potential interaction between drugs used in combination therapy should be investigated. The efficacy of PAH treatments in randomized clinical trials is measured by means of a number of different surrogate endpoints. For example, the exercise capacity of patients is assessed with the distance walked in 6 minutes, known as the 6-minute walk distance (6MWD). Symptomatic severity is summarized using the World Health Organization functional class (WHO FC), with patients in WHO FC I being the least symptomatic and those in WHO FC IV the most severely affected. However, because PAH patients have impaired cardiac function and because hemodynamic parameters are a central part of PAH diagnosis and management, great importance is placed on these measurements. They are also the only measurements that can be used as endpoints in an acute setting. Pulmonary vascular resistance, for instance, measures the resistance to blood flow exerted by the vasculature in the lungs.

The pharmacodynamic consequences of reduced plasma sildenafil concentrations in combination with bosentan have not yet been evaluated in a clinical trial. The primary objective of the COMPASS-1 study was to explore the acute hemodynamic effects of sildenafil administration in patients with PAH who are already receiving bosentan treatment.

METHODS

Patient Population

Patients aged ≥18 years, with symptomatic PAH in WHO FC II or III who were already receiving bosentan as maintenance therapy, were eligible for inclusion into the study. Patients with idiopathic PAH, familial PAH, and PAH associated with corrected congenital systemic-to-pulmonary shunts or drugs or toxins were included. PAH had to be diagnosed or reconfirmed by right heart catheterization within 24 months prior to enrollment, with mean pulmonary arterial pressure (mPAP) ≥25 mm Hg and pulmonary artery occlusion pressure (PAOP) ≤15 mm Hg.[18]

Patients were required to have documented nonresponsiveness to vasoreactivity testing within 24 months prior to enrollment but before commencing bosentan therapy. Patients were also required to have received bosentan 125 mg bid as monotherapy for PAH for ≥12 weeks before enrollment. To participate in the study, patients had to have been stable for ≥12 weeks before enrollment, be able to undergo right heart catheterization for 2 to 3 hours, and have a PVR at baseline on the day of the right heart catheterization measurements of ≥320 $dyn \cdot s \cdot cm^{-5}$. The minimum value of PVR was chosen to allow the possible detection of a clinically relevant reduction following treatment. The upper normal threshold for PVR in healthy adult participants is 50 to 150 $dyn \cdot s \cdot cm^{-5}$.[19]

Patients were excluded from the study if they were diagnosed with PAH due to causes other than those listed above, planned to receive treatment with epoprostenol, or had suspected pulmonary

veno-occlusive disease. Patients with systolic blood pressure <85 mm Hg, body weight <40 kg, hemoglobin <75% of the lower limit of the normal range, serum concentrations of alanine and aspartate aminotransferases >3 times the upper limit of the normal range, or moderate to severe hepatic impairment were also excluded. Use of PAH drugs (endothelin receptor antagonists other than bosentan, PDE-5 inhibitors, prostanoids, nitric oxide, and L-arginine) or calcineurin inhibitors within 3 months prior to enrollment was not permitted. Use of anticoagulants and diuretics was permitted, and center-specific guidelines for restriction/withdrawal were followed on the day of right heart catheterization.

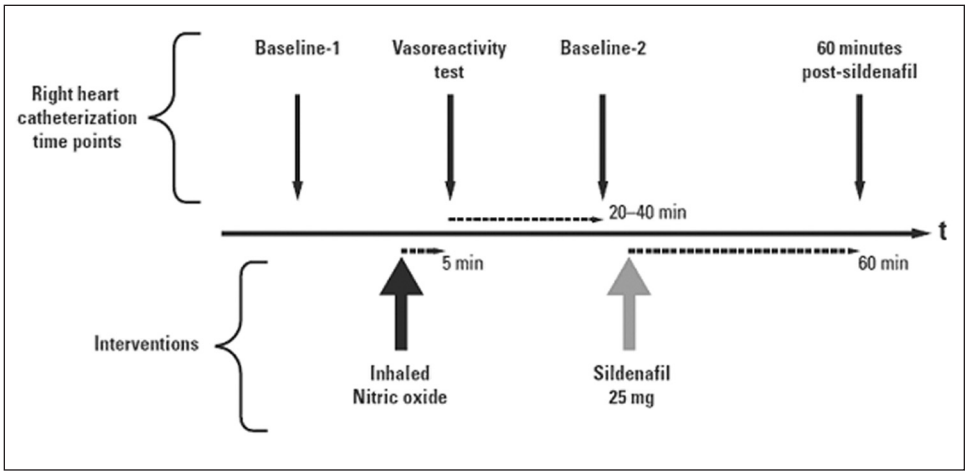

Figure 2. Schedule of interventions and hemodynamic assessments.

Study Design

This was a prospective, open-label, noncomparative, multicenter, phase II study, designed to investigate the hemodynamic effect of an acute, single dose of sildenafil (25 mg) in patients already receiving bosentan for ≥12 weeks.

Patients were screened within 14 days prior to the administration of the single dose of sildenafil. After the day of right heart catheterization and sildenafil treatment, patients were followed up for 28 days.

On the treatment day, a Swan-Ganz catheter was inserted through the right jugular or subclavian vein and placed into either the right or left pulmonary artery. In this study, bosentan was in steady-state conditions, both from a pharmacokinetic and pharmacodynamic point of view.[14] The last bosentan dose was administered between 7 and 16 hours before treatment with sildenafil. Patients were asked not to eat at least 4 hours before sildenafil administration because food intake influences the pharmacokinetics of sildenafil.[6] Prescribed or over-the-counter drugs or food constituents with a CYP-inducing or CYP-inhibiting effect (including St John's wort and grapefruit juice) were avoided during this study. All efforts were made to ensure that right heart catheterization was always performed by the same investigator in all patients at each study center. Patients were assessed at the following 4 time points (Figure 2):

Baseline 1: Right heart catheterization measurements

Vasoreactivity testing: Performed with inhaled nitric oxide (iNO) according to the guidelines of the European Society of Cardiology (iNO at 10-20 ppm for 5 minutes; definition of vasoreactivity: reduction of mPAP ≥10 mm Hg to reach an absolute value of mPAP ≤40 mm Hg with an increased or unchanged cardiac output [CO]),[15] followed by right heart catheterization measurements

Baseline 2: Right heart catheterization measurements before the administration of a single dose of sildenafil (25 mg) (time 0). Measurements at baseline 2 were conducted between 20 and 40 minutes after the vasoreactivity test.

Sixty minutes after sildenafil: Final right heart catheterization measurements, followed by catheter removal

At each of the 4 time points, measurements of mPAP, PAOP, and CO were recorded until the last of 2 consecutive values differed from the first by ≤10%. The last value was recorded. CO was measured by the thermodilution method according to the established practice in each center; the maximum number of CO measurements was 3. The derived hemodynamic parameters, PVR, total pulmonary resistance (TPR), and systemic vascular resistance were calculated using the following formulas: PVR = (mPAP − PAOP)*80/CO, TPR = mPAP*80/CO, and SVR = (mean systemic arterial pressure − mRAP)*80/CO. Heart rate was monitored continuously by 12-lead electrocardiogram.

Systemic arterial pressures were measured noninvasively by using an arm cuff and sphygmomanometer at the brachial artery. All hemodynamic evaluations were performed in the supine position. Plasma N-terminal prohormone B-type natriuretic peptide (NT-proBNP) concentrations were determined in all centers using the same validated point-of-care test (Cardiac Reader, Roche Diagnostics, Switzerland).

This study was conducted in full compliance with the most recent amendment of the Declaration of Helsinki and good clinical practice guidelines and was approved by the ethics committees of all participating centers. Written informed consent was obtained from all patients prior to inclusion in the study.

Efficacy Endpoints

The primary efficacy endpoint was reduction in PVR from baseline 2 to 60 minutes after sildenafil administration, expressed as percent change from baseline 2. Secondary efficacy endpoints were reduction in TPR and NT-proBNP from baseline 2 to 60 minutes after sildenafil administration, expressed as percent change from baseline 2. Vasoreactivity to iNO was reassessed on the treatment day. All other efficacy variables (mPAP, PAOP, CO, systemic vascular resistance, PVR/systemic vascular resistance) and all analyses of the effects of iNO were exploratory in nature.

Safety Endpoints

Safety was evaluated by monitoring adverse events, serious adverse events, and changes in vital signs and 12-lead electrocardiogram. The intensity of adverse events was graded as mild, moderate, or severe, and all adverse events were assessed by the investigators as to whether they were related either to sildenafil or bosentan.

Statistical Analyses

Sample size was calculated based on the primary efficacy endpoint. A total of 44 evaluable patients were required to detect with a power of 90% a mean change in PVR from baseline 2 to 60 minutes after sildenafil of ≥10%, assuming a standard deviation of 20% with the data being normally distributed.

The main analysis of the primary efficacy endpoint was performed using the 1-sample Student *t* test on the per-protocol set (excluding patients with major protocol deviations) with supportive and exploratory analyses being performed on the all-treated set. The corresponding 95% confidence limits (CLs) for the mean percent change were calculated with the quantile of the *t* distribution. The 2-sided Type I error was 0.05. No imputation rules for missing data were applied.

The acute pharmacodynamic response to sildenafil was compared with that of iNO in patients with complete PVR assessments at all right heart catheterization time points.

Correlations between baseline characteristics (age, duration of PAH, time since start of bosentan, 6MWD, Borg dyspnea index, NT-proBNP, PVR) were tested using Spearman's correlation coefficient. Univariate analyses were performed to explore the potential

Table I Patient Demographics and Disease Characteristics (All-Enrolled Set; n = 45)

	Sildenafil (n = 45)
Patient demographics	
Female gender, n (%)	34 (75.6)
Age, y	52.6 ± 15.2
Weight, kg	76.9 ± 20.7
Height, cm	164.1 ± 7.9
Ethnicity, n (%)	
White	43 (95.6)
Black	1 (2.2)
Hispanic	1 (2.2)
Baseline characteristics	
Duration of PAH, months	30.3 ± 28.8
Time since start of bosentan, months	21.9 ± 15.9[a]
Etiology of PAH, n (%)	
Idiopathic PAH	36 (80.0)
Familial PAH	3 (6.7)
Related to corrected congenital shunts	2 (4.4)
Related to drugs or toxins	4 (8.9)
6-minute walk distance, m	408.9 ± 107.3[b]
WHO FC, n (%)	
FC II	19 (42.2)
FC III	26 (57.8)
Borg dyspnea index	4.7 ± 2.4
PVR, dyn·s·cm^{-5}	836.9 ± 629.2[c]
TPR, dyn·s·cm^{-5}	1086.5 ± 740.5[d]
CO, L/min	4.3 ± 1.4[d]
Cardiac index, L/min/m^2	2.4 ± 0.7[c]
mPAP, mm Hg	48.7 ± 15.7[d]

Values are mean ± standard deviation unless specified otherwise. CO, cardiac output; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; TPR, total pulmonary resistance; WHO FC, World Health Organization functional class.
a. n = 44.
b. n = 43.
c. n = 36.
d. n = 37.

Table II Mean PVR at All Time Points

	Per-Protocol Set (n = 37)	Patients With PVR Values at All Time Points (n = 32)
Mean PVR at baseline 1, dyn·s·cm^{-5}	815[a] (587, 1043)	807 (578, 1036)
Mean PVR following iNO, dyn·s·cm^{-5}	753[a] (487, 1019)	745 (478, 1011)
Mean percent change, baseline 1 to iNO	–15*[a] (–21, –8)	–15* (–22, –8)
Mean PVR at baseline 2, dyn·s·cm^{-5}	889 (656, 1121)	829 (568, 1089)
Mean PVR 60 minutes after sildenafil, dyn·s·cm^{-5}	778 (561, 995)	721 (487, 956)
Mean percent change, baseline 2 to 60 minutes after sildenafil	–15* (–21, –10)	–15* (–22, –9)

Data are shown with 95% confidence limits in parentheses. PVR, pulmonary vascular resistance; iNO, inhaled nitric oxide.
a. $n = 32$.
*$P \leq .0001$.

influence of baseline characteristics (age, sex, etiology, WHO FC, duration of PAH, time since start of bosentan, 6MWD, Borg dyspnea index, NT-proBNP, PVR) on percent change in PVR, with use of the Spearman's correlation coefficient for continuous baseline characteristics and the Kruskal-Wallis test for categorical baseline characteristics.

RESULTS

Patient Characteristics

A total of 45 patients were enrolled at 12 centers in 5 countries: Germany (6 centers), Italy (2 centers), Canada (2 centers), Belgium (1 center), and the Netherlands (1 center). There was 1 patient who did not receive treatment for failure to meet the inclusion criteria. The remaining 44 patients completed the study and comprise the all-treated analysis set. Four patients had major protocol deviations (last food intake <4 hours before baseline 1 [n = 3]; last bosentan dose before baseline 1 outside of time window of 7-16 hours [n = 1]) and were excluded from the per-protocol analysis set (n = 40). Missing PAOP data resulted in the exclusion of additional patients from per-protocol sets for specific endpoints.

Baseline demographics and disease characteristics for all patients are presented in Table I. Prior and concomitant diseases were consistent with those of patients taking bosentan for PAH. The most frequent concomitant medications were furosemide (38%), torasemide (31%), and the anticoagulant phenprocoumon (31%).

Hemodynamic Effects

Table II shows the observed changes in PVR for patients who had PVR values for all time points and for the per-protocol analysis set. A reduction in TPR of –9% (95% CL: –13.5, –5; $P < .0001$) was also observed, from 1111 dyn·s·cm^{-5} (95% CL: 852, 1370) at baseline 1 to 1036 dyn·s·cm^{-5} (95% CL: 772, 1300) following iNO administration. Of 35 patients undergoing acute vasoreactivity testing, only 1 patient was a responder according to the PAH guidelines definition.[18]

There was a significant reduction in PVR with a mean percent change of –15% (95% CL: –21%, –10%; $P < .0001$; n = 37) from baseline 2 to 60 minutes after sildenafil in the per-protocol analysis set (Table II). For TPR, a reduction from 1128 dyn·s·cm^{-5} (95% CL: 881, 1374) at baseline 2 to 986 dyn·s·cm^{-5} (95% CL: 765, 1206) 60 minutes after sildenafil was observed (–13% change; 95% CL: –17%, –10%; $P < .0001$; n = 40). These changes in PVR and TPR were based on a mean percent decrease in mPAP of –9% (95% CL: –12%, –6%; $P < .0001$; n = 40) and a mean percent increase in CO of 6% (95% CL: 2%, 9%; $P = .0026$; n = 40). No significant change in PAOP was observed.

A total of 32 patients had complete PVR assessments at all time points (baseline 1, vasoreactivity testing, baseline 2, and 60 minutes after sildenafil). For the remaining patients, PVR could not be calculated at all time points because of missing PAOP values. PAOP data were available for 36 patients at

baseline 1, 33 patients at vasoreactivity testing, 40 patients at baseline 2, and 41 patients 60 minutes after sildenafil treatment. The reduction in mean PVR after administration of sildenafil was of a similar magnitude to that observed following administration of iNO (Table II). The same was true for the reduction in mPAP by these 2 agents.

Biomarker Outcomes

NT-proBNP did not change significantly following administration of sildenafil (mean increase +6%; 95% CL: –1%, 13%; $P = .0883$; n = 37). Plasma concentrations of NT-proBNP at baseline correlated positively with baseline PVR (Spearman correlation coefficient 0.42; $P = .0118$; n = 36, per-protocol set) and negatively with baseline 6MWD (Spearman correlation coefficient –0.42; $P = .0094$; n = 37, per-protocol set). There were no other significant correlations between the baseline characteristics, and none of them had a significant influence on the percent change in PVR after administration of sildenafil.

Safety

A total of 11 adverse events were reported in 7 patients. Of these, 6 adverse events in 2 patients were considered related to sildenafil (insomnia, nausea, migraine, and dizziness in 1 patient and dry mouth and nasal congestion in another patient). The other adverse events were supraventricular extrasystoles, headache, dyspnea exacerbated, cystitis, and hemorrhage. No adverse event was considered related to bosentan or right heart catheterization. No serious adverse events were observed.

Mean changes in systolic blood pressure and systemic vascular resistance of –4% (95% CL: –7%, –2%; $P < .0026$; n = 40) and –9% (95% CL: –13%, –6%; $P < .0001$; n = 39), respectively, were observed from baseline 2 to 60 minutes after sildenafil treatment. The change in PVR/systemic vascular resistance ratio over this period was –5% (95% CL: –11%, 1%; $P = .1171$; n = 36).

DISCUSSION

In this prospective, open-label, noncomparative study, the acute administration of sildenafil to patients with PAH and ongoing bosentan therapy led to a significant decrease in PVR. The reduction in PVR was of a magnitude comparable to that observed following inhalation of NO. A reduction in TPR and mPAP and an increase in CO were also observed following the administration of sildenafil. No significant changes were observed in PAOP or concentrations of NT-proBNP. These results demonstrate that sildenafil exerts significant acute effects on cardiopulmonary hemodynamics in patients on chronic bosentan therapy. These findings support the hypothesis that the simultaneous targeting of the endothelin- and NO-mediated pathways may result in additional favorable effects.

PVR was chosen as the primary endpoint in this study, as it plays an important role in the management of PAH and has been used in many other clinical trials of PAH therapy. The observed reduction in PVR of –15% is in the range of the hemodynamic effects exerted by sildenafil alone in treatment-naive patients. In a previous study, oral administration of 75 mg sildenafil decreased PVR by –27% after 50 minutes,[20] at which time point the hemodynamic effects of sildenafil have been found to reach their maximum.[21] In another study, a decrease in PVR of –22% was observed 60 minutes following oral administration of 50 mg sildenafil.[22] In a third study, a decrease in PVR of –15% was observed after administration of 2 × 50-mg sildenafil doses at a 30-minute interval.[23] A fourth study measured a reduction in PVR of –15% 60 minutes after administration of 12.5 mg sildenafil.[24] Interestingly, similar hemodynamic improvements in PVR of –12% were also observed in the SUPER-1 study after 12 weeks of sildenafil monotherapy at the approved dose for PAH of 20 mg tid.[25] Despite differences in dosing or design, the hemodynamic improvements by sildenafil alone as reported in the studies described above were very comparable to those observed in the present study. Other randomized clinical trials with other PAH therapies have demonstrated changes of similar magnitude, which are regarded as clinically relevant.[11,26-28]

These observations suggest that the reported pharmacokinetic interaction between bosentan and sildenafil[13,17] may not influence the acute pharmacodynamic effects of sildenafil in PAH patients treated with bosentan. Therefore, as known for other drug-drug combinations,[29] reductions in exposure to sildenafil, when given on top of bosentan treatment, may not necessarily translate into hemodynamic consequences. However, whether the relatively flat dose-response curve of sildenafil monotherapy changes upon combination treatment with bosentan and other PAH drugs has not yet been studied. We look forward to future randomized clinical trials generating further data on the efficacy of this combination of drugs.

Results from a number of clinical trials provide supportive evidence that sildenafil, when combined with bosentan, may exert additional long-term clinical benefits. In an uncontrolled, open-label, nonrandomized study, 9 patients with idiopathic PAH who received sildenafil in addition to bosentan monotherapy exhibited improvements in exercise capacity that were maintained at a median follow-up of 9 months.[9] In a further uncontrolled study of 11 patients with either idiopathic PAH or PAH associated with congenital heart disease,[30] the combination was related to a decrease in mean pulmonary arterial pressure over a median of 1.1 years. Recently, Mathai and colleagues[10] observed beneficial effects of bosentan and sildenafil in combination in a small number of patients with scleroderma-associated PAH, and another study by Porhownik et al[31] demonstrated an improvement of exercise capacity 6 months after initiation of combination therapy. In the recent EARLY study of bosentan versus placebo in PAH patients in WHO FC II, a reduction in PVR of –20% was observed in patients who received bosentan in addition to ongoing sildenafil treatment.[11] However, until results from randomized clinical trials are available, it will not be possible to judge whether the effect versus time course of sildenafil monotherapy differs from the effects in combination with bosentan. The currently ongoing morbidity/mortality study (COMPASS-2) evaluating the combination of bosentan and sildenafil versus sildenafil monotherapy will generate additional information pertaining to the clinical relevance of this combination in the future.

In the present study, although only the hemodynamic effects of an acute, single dose of sildenafil in the presence of bosentan were explored, these are not expected to differ markedly from those of chronic treatment. First, following multiple dosing regimens, sildenafil exposure is not significantly higher than following single dosing.[13,32] Second, the extent of PVR reduction was very similar in the SUPER-1 study after 12 weeks of sildenafil 20 mg tid.[25] This may suggest that no tolerance develops to the hemodynamic effects of sildenafil over this timeframe, based on an interstudy comparison.

In addition to PVR, TPR was analyzed to address a potential effect of sildenafil on PAOP and thus on the primary endpoint, PVR, independently of its effect on pulmonary arteries. However, PAOP was not observed to be increased, in accordance with results from a previous study.[20]

Vasoreactivity testing was performed to assess its possible restoration in previous nonresponders following bosentan therapy. Only 1 patient exhibited a restoration of acute vasoreactivity in response to iNO administration, suggesting that pulmonary vasoreactivity is generally not restored following treatment with bosentan for at least 12 weeks. Consequently, the usefulness of repeating the vasoreactivity test in previous nonresponders is questionable.

No substantial changes were observed in the plasma levels of NT-proBNP after 60 minutes. NT-proBNP is a cardiac neurohormone that is secreted from the ventricles in response to ventricular pressure overload characteristic of PAH and certain other cardiac diseases.[33,34] As this peptide has been found to differ between responders and nonresponders during a 60-minute challenge with iNO,[35] the current study explored if it would change in parallel with the anticipated acute hemodynamic response to sildenafil 60 minutes after application. The absence of changes in plasma levels of NT-proBNP observed in this study are in accordance with the findings of Souza et al,[35] who did not observe substantial changes in NT-proBNP levels in patients who were not responsive to iNO after 60 minutes of sustained inhalation. These observations may be related to the estimated 120-minute half-life of NT-proBNP,[36] in comparison with the short observation period of 60 minutes in our study and that of Souza et al.[35]

Baseline NT-proBNP correlated with baseline PVR and baseline exercise capacity in this population of PAH patients treated with bosentan. This may support the concept that NT-proBNP plasma levels represent a marker of disease severity in PAH patients.

The addition of oral sildenafil in combination with ongoing bosentan treatment in patients with PAH was well tolerated. This is in accordance with the results from the bosentan postmarketing surveillance, which did not identify any potential safety concerns associated with the combination of bosentan and sildenafil.[12]

Limitations of this study include the open-label design and absence of a placebo control. Nevertheless, the assessment of vasoreactivity using iNO provides a positive control. Further limitations of the study include the use of only 1 dose of sildenafil and the measurements of effects at a single time point only (ie, 60 minutes after sildenafil). Hence, the pharmacodynamic information that can be derived from the study is limited and does not allow conclusions to be drawn about dose/concentration-response relationships or the time course of sildenafil effects when given in combination with bosentan. Another limitation is the chosen dose of sildenafil (25 mg), as

the dose of sildenafil currently approved for management of PAH (20 mg tid) was not yet available when this study was designed. However, the chosen and approved doses of sildenafil are similar, and no marked pharmacodynamic differences between these 2 doses in the acute setting would be anticipated. Pharmacokinetic determinations were not conducted in this study because the effects of bosentan on the pharmacokinetics of sildenafil have been assessed accurately and were reported to be very consistent between healthy participants and patients with PAH.[13,17] The broad time window between last bosentan dose and sildenafil administration was chosen to allow the effects of sildenafil to be explored when bosentan plasma concentrations were at or close to their trough levels. These levels are expected to be associated with lower variability in pharmacodynamic effects of bosentan than those assessed at peak, although knowledge concerning the relationship between pharmacokinetics and pharmacodynamics of bosentan is limited.[14] Furthermore, the enzyme induction properties of bosentan should not be influenced by plasma concentration of bosentan. During a chronic dosing regimen of bosentan, such as that seen in this study, these properties do not depend on the plasma concentrations of bosentan but rather on the half-life of the enzymes that are induced by bosentan, which is at least 24 hours.[37] A post hoc correlation analysis confirmed that the time since last dose had no influence on the change in PVR (Spearman coefficient = 0.10, $P = .54$; data not shown).

CONCLUSION

The results of the COMPASS-1 study demonstrate that a single dose of sildenafil elicits a significant acute hemodynamic effect when added to long-term bosentan therapy in PAH patients. Despite the known drug-drug interaction, the hemodynamic data generated indicate that the combination of the 2 drugs might bring additional clinical benefits to PAH patients. In this acute setting, combination of sildenafil and bosentan resulted in no safety concerns. This may represent a rationale for long-term combination studies with the 2 compounds.

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