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Clinical research

Clinical and haemodynamic effects of sildenafil in pulmonary hypertension: acute and mid-term effects

Ghada W. Mikhail[a], Sanjay K. Prasad[a], Wei Li[a], Paula Rogers[a], Adrian H. Chester[b], Stephanie Bayne[a], David Stephens[c], Mohammed Khan[b], J.S.R. Gibbs[d], Timothy W. Evans[a], Andrew Mitchell[a], Magdi H. Yacoub[b], Michael A. Gatzoulis[a,*]

[a] *Adult Congenital Heart Unit, Royal Brompton and Harefield NHS Trust, Sydney Street, London SW3 6NP UK*
[b] *National Heart and Lung Institute, Imperial College of Science, Technology and Medicine, London, UK*
[c] *Imperial College of Science, Technology and Medicine, London, UK*
[d] *National Heart and Lung Institute, Imperial College of Science, Technology and Medicine and Hammersmith Hospitals NHS Trust, London, UK*

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Aim The treatment of patients with pulmonary arterial hypertension remains a challenge. We set out to investigate the use of sildenafil, a selective inhibitor of phosphodiesterase type 5, in patients with this disease.
Methods and results Ten patients (8 females, mean age 34.5 ± 3.3 years) with pulmonary hypertension underwent right heart catheterisation with vasodilator testing using incremental doses of intravenous sildenafil without adverse events. All patients were subsequently commenced on oral sildenafil 50 mg t.d.s. Nine patients had repeat right heart catheterisation 3 months after the commencement of oral therapy. There was a significant reduction in mean pulmonary artery pressure (from 55.8 ± 5.9 to 50.4 ± 6.1 mmHg, $p = 0.038$) and pulmonary vascular resistance (from 10.1 ± 1.7 to 8.6 ± 1.5 Wood units, $p = 0.009$), and an increase in cardiac output (from 4.7 ± 0.3 to 5.0 ± 0.4 l/min, $p = 0.15$). Furthermore, there was a significant increase in the 6-minute walk test, a mean of 112 m. In response to a quality-of-life questionnaire, patients indicated marked clinical improvement on sildenafil. Sildenafil was discontinued in 1 patient due to a transient visual disturbance. The only patient previously awaiting transplantation was removed from the active transplantation list.
Conclusions Sildenafil is well tolerated in its intravenous and oral forms and appears to improve both pulmonary haemodynamics and the clinical status of patients with pulmonary hypertension after 3 months of oral therapy.

Introduction

Pulmonary arterial hypertension is a progressive disease with a poor prognosis that ultimately leads to right ventricular failure and death. Although therapeutic

* Corresponding author. Tel.: +44-207-351-8602; fax: +44-207-351-8629.
E-mail address: m.gatzoulis@rbh.nthames.nhs.uk (M.A. Gatzoulis).

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options continue to evolve, the treatment of patients with the severe form of the disease remains a challenge. Present therapeutic applications have limitations including the delivery mechanism (e.g., IV epoprostenol), short half-life (e.g., inhaled iloprost), and cost.[1,2] There has been recent interest in the potential role of novel therapies including sildenafil, a selective inhibitor of phosphodiesterase type 5.[3] Sildenafil decreases the degradation of cyclic guanosine monophosphate (GMP) and promotes the release of nitric oxide, resulting in vasodilation.[4] Sildenafil has been shown to act as a pulmonary vasodilator in animals with experimentally induced pulmonary hypertension.[5,6] It appears to attenuate hypoxia-induced pulmonary hypertension in both humans and mice.[5] Following our anecdotal experience with a young adult patient with severe pulmonary arterial hypertension who had a dramatic response to therapy with oral sildenafil,[7] we set up the present study to examine the safety and efficacy of intravenous and oral sildenafil therapy in the management of patients with pulmonary hypertension.

Methods

Patients

We investigated 10 consecutive patients with pulmonary hypertension whose baseline characteristics are shown in Table 1. This was an intention-to-treat, open-label, non-randomised study. The study was approved by the local ethics committee and written informed consent was obtained from all patients. Patients were admitted to the hospital for a period of one week for initial baseline assessment, including cardiac catheterisation, followed by the introduction and titration of oral sildenafil. Sildenafil was added to the patients' existing medical therapy. None of the patients recruited in our study had been previously treated with pulmonary vasodilators such as iloprost or bosentan.

Table 1 Baseline demographics data

N	10
Age	
Range	20—60 years
Mean	34.5 ± 3.3 years
Sex	
M:F	2:8
Aetiology	
PAH (Sporadic)	7 (70%)
Chronic thromboembolic disease	1 (10%)
Related to collagen vascular disease	1 (10%)
Drugs/toxin	1 (10%)
Baseline medications	
Warfarin	10 (100%)
Calcium channel antagonist	4 (40%)
Diuretic	6 (60%)
NYHA functional class	
I	0
II	5
III	5
IV	0
6-min walk (m)	283 ± 47

PAH, pulmonary arterial hypertension.

Investigations

Baseline investigations included a transthoracic echocardiogram, a 6-minute walk test, and cardiopulmonary exercise testing[8] to assess maximum oxygen uptake (MVO_2) and ventilatory efficiency by means of the VE/VCO_2 ratio.[9] Comprehensive echocardiographic assessment of cardiac function and haemodynamic response to sildenafil included right ventricular (RV) and left ventricular (LV) dimensions, Doppler calculations of isovolumic relaxation time (IVRT), tricuspid regurgitation pressure gradient (TRPG), tricuspid valve inflow time (TVIT), tricuspid regurgitation (TR) time, maximum velocity across aortic valve (Vao), aortic ejection time (AoET), Vmax pulmonary artery, pulmonary artery acceleration time (PAAcT), and pulmonary artery ejection time (PAET).[10–12] Patients completed a quality-of-life questionnaire known as the Short-Form Health Survey (SF-36).[13] At cardiac catheterisation, measurements of right atrial pressure (RAP), RV pressure, pulmonary artery pressure (PAP), and LV systolic and end-diastolic pressures were obtained. Pulmonary and systemic arterial oxygen saturations were measured. Cardiac output (CO) was calculated using the Fick principle. Acute vasodilator testing was carried out using incremental doses of intravenous sildenafil (1 mg/ml) at infusion rates of 2 ml/h initially and then 9 and 16 ml/h to achieve plasma levels of 100, 300, and 500 ng/l, respectively (equivalent to peak plasma levels of 25, 50, and 100 mg of oral sildenafil therapy). Each dose was administered by peripheral continuous infusion for a period of 20 min. Haemodynamic measurements were made at baseline and at the end of each intravenous dose increment. All patients recruited in this study received vasodilator testing only with IV sildenafil and none of the patients had previous haemodynamic reversibility studies carried out with oxygen, acetylcholine, or iloprost.

Oral sildenafil

Following baseline assessment, patients were commenced on 25 mg of oral sildenafil (irrespective of pulmonary vasodilator response to intravenous sildenafil). The dose was titrated to a maintenance dose of 50 mg t.d.s. in all patients prior to discharge. At 3 months, patients were readmitted and all baseline measurements, including cardiac catheterisation, were repeated.

Statistical analysis

Results are quoted as means ± SE. The non-parametric Friedman rank sum test was used to check the dose effect of IV sildenafil on the mean PAP, CO, and pulmonary vascular resistance (PVR) separately. The non-parametric Wilcoxon signed-rank test was used to compare baseline and 3-month follow-up data (invasive haemodynamics, transthoracic echocardiography, and exercise indices). The Spearman rank correlation coefficient was used to determine the relationship between the acute and 3-month response to sildenafil. All analyses were blinded from clinical data. A $p < 0.05$ was considered significant.

Results

None of the patients died during the study. Complete follow-up data were obtained in 9/10 patients. Sildenafil was discontinued after 2 months of therapy in one patient because of transient blurred vision (which resolved within hours of discontinuing sildenafil). No other serious acute or chronic adverse events were observed. No additional medication for pulmonary hypertension was required during the study. The single patient from this cohort awaiting transplantation prior to initiation of sildenafil therapy improved to the point that the patient was removed from the active transplantation list at the end of the study.

Symptoms and exercise capacity

Four patients in NYHA class III showed improvement in functional class (3 improved to class II and 1 improved to class I). Overall, 7/9 patients (78%) demonstrated improvement in overall health and well-being. Improvement was also noted in physical activity and patients stated that by the end of the study they were able to climb stairs and walk longer distances. Improved physical ability was associated with an improved emotional status and improvement in mood. The 2 remaining patients (22%) reported no overall symptomatic change.

There was a significant increase in the 6-minute walk test (from 283 ± 47 to 395 ± 33 m, $p = 0.018$) (Fig. 1) between baseline and 3 months. There was no significant change in MVO2 (14.8 ± 1.6 at baseline to 15.1 ± 1.2 ml/kg/min, $p = 0.088$) (Fig. 2) or ventilatory efficiency measured by the V_E/V_{CO_2} slope (from 47.7 ± 5.9 to 46.1 ± 5.2, $p = 0.084$) at 3 months compared to baseline.

Haemodynamic data (Table 2)

Acute response

There were no adverse events or any haemodynamic compromise with incremental doses of IV sildenafil. There was a significant dose effect of IV sildenafil on mean PAP ($p = 0.00028$), PVR ($p = 0.0016$), and CO ($p = 0.014$) (Figs. 3(a)–(c)).

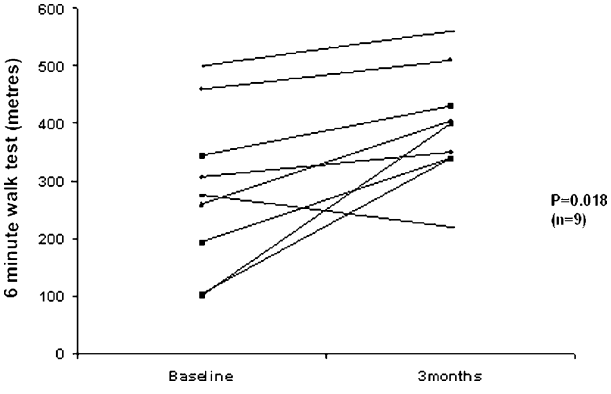

Fig. 1 Six-minute walk test: Data from baseline and after 3 months of oral sildenafil administration.

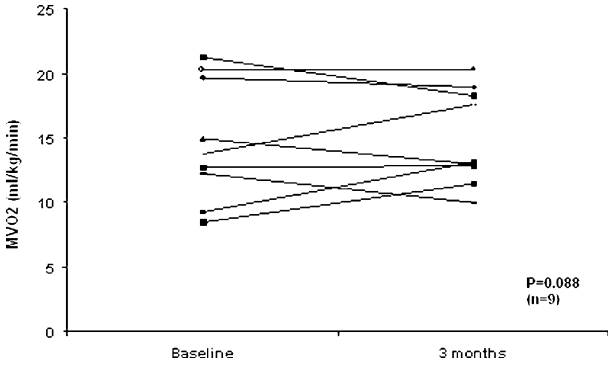

Fig. 2 Maximum oxygen consumption (MVO2): Data from baseline and after 3 months of oral sildenafil administration.

At 3 months

There was a significant reduction in systolic PAP, mean PAP, PVR, and PVRI (index) and a trend towards an increase in CO after 3 months of oral sildenafil therapy, compared to baseline (Fig. 4). In contrast, there was no significant reduction in systemic arterial pressure (systolic, from 125.3 ± 8.6 to 119.4 ± 7.6 mmHg, $p = 0.071$) during the study period.

Baseline acute haemodynamic response to incremental doses of IV sildenafil was not predictive of mid-term response in pulmonary haemodynamics after 3 months of oral sildenafil therapy. The correlation coefficient was −0.43 for the maximal change in mean PAP following IV sildenafil at baseline compared to the response after 3 months of oral therapy. There was no significant effect on the PVR/systemic vascular resistance (SVR) ratio after 3 months compared to baseline ($p = 0.087$). There was a significant increase in pulmonary artery oxygen saturation between baseline and 3 months ($p = 0.037$). Systemic arterial saturations also increased, albeit this was not significant (Table 2).

Echocardiography (Table 2)

At 3 months, there was a significant increase in PAAct measured by Doppler. There was a non-significant trend towards improvement in both RV and LV function. However, there was no change in estimated RV pressure as derived from tricuspid regurgitation.

Discussion

This study has shown that administration of sildenafil in its intravenous and oral form to patients with pulmonary hypertension is safe. Three months of oral therapy with sildenafil led to improved functional class, exercise capacity, and haemodynamics with no systemic disturbance.

There has been recent interest in the role of oral therapies for pulmonary hypertension, such as phosphodiesterase-selective inhibitors and endothelin antagonists.[14] Other groups have recently reported preliminary data on sildenafil; Zhao et al.[5] showed that 100 mg of sildenafil attenuates hypoxia-induced pulmonary hypertension in experimental work on humans and on mice.[5]

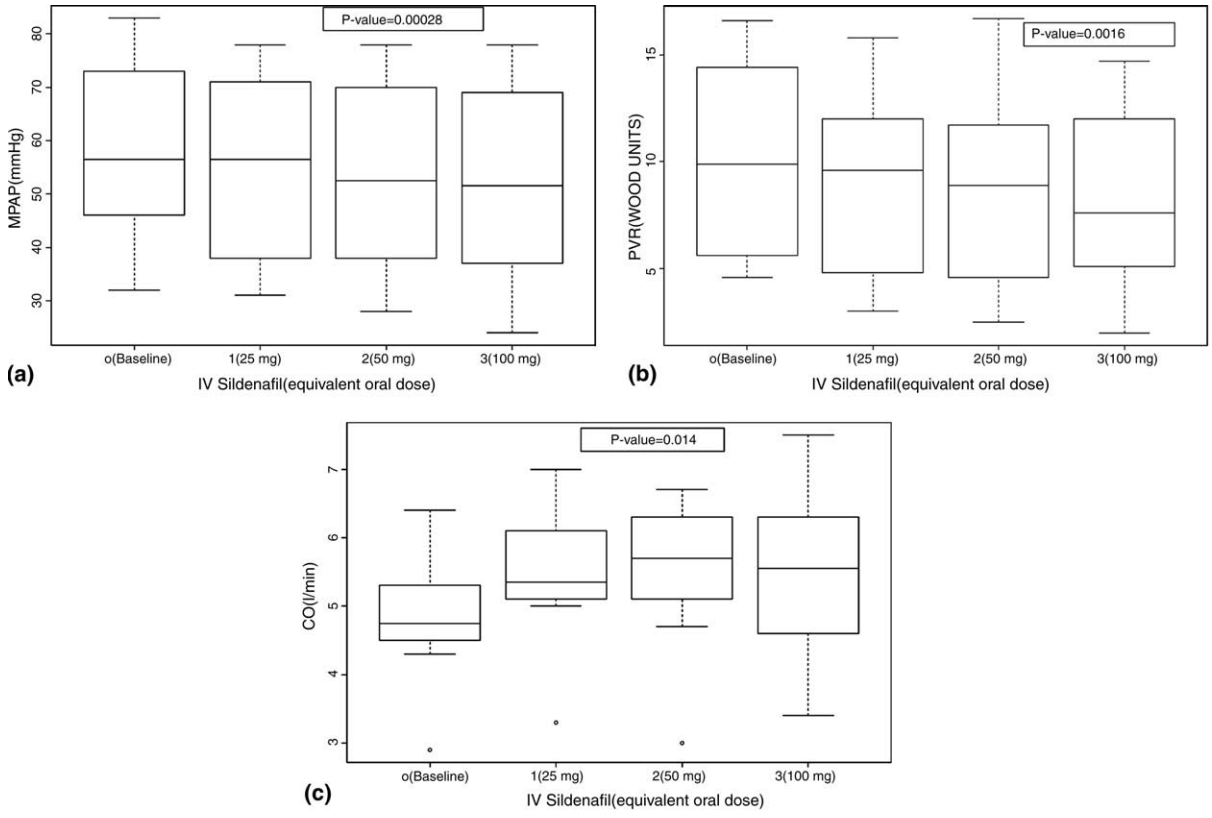

Fig. 3 Changes with incremental doses of intravenous sildenafil during right heart catheterisation at baseline. (a) Mean pulmonary artery pressure (MPAP); (b) Pulmonary vascular resistance (PVR); (c) Cardiac output (CO).

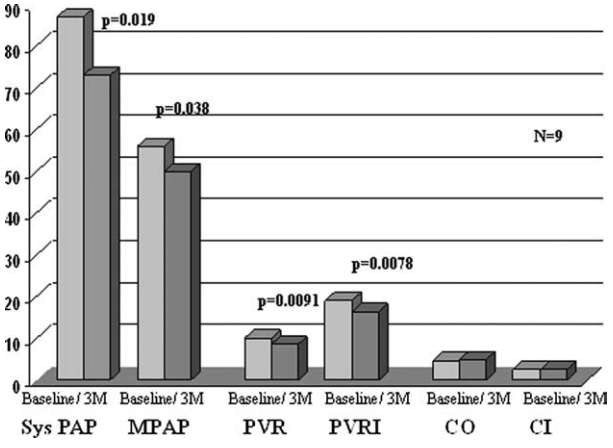

Fig. 4 Invasive haemodynamics (systolic PAP, mean PAP, PVR, pulmonary vascular resistance index [PVRI], CO, and cardiac index [CI]): Data from baseline and after 3 months of oral sildenafil administration.

The eNOS-NO-cGMP (endothelial nitric oxide synthase-nitric oxide-cyclic guanosine monophosphate) pathway is thought to be primarily responsible. Michelakis et al.[15] demonstrated that oral sildenafil as a single dose acts as a potent pulmonary vasodilator in patients with both primary and secondary pulmonary hypertension. Compared with inhaled NO, oral sildenafil was found to be superior in decreasing PAP and was as effective as NO in reducing PVR. There is also evidence for a favourable acute haemodynamic response to sildenafil in pulmonary arterial hypertension when used in conjunction with inhaled iloprost.[16] Finally, Sastry et al.[17] reported the clinical efficacy of oral sildenafil in patients with primary pulmonary hypertension using 100 mg t.d.s. over a 3-month period. However, this was a non-invasive study without direct catheter assessment of haemodynamics at baseline and during follow-up.

Our study was designed to assess both the acute and mid-term effects of sildenafil. Our haemodynamic data suggest that intravenous sildenafil is safe in the acute setting. Intravenous sildenafil did not lead to systemic disturbances nor was it responsible for any haemodynamic compromise during cardiac catheterisation. There was a significant dose effect on haemodynamic measurements of PAP, PVR, and CO. Although there was a range of acute haemodynamic responses to intravenous sildenafil, this was not predictive of subsequent response to mid-term oral sildenafil therapy. The latter may reflect time-related remodelling of the pulmonary vasculature in pulmonary hypertension.[18,19] While our data need to be interpreted with caution, because of the small number of patients studied, they indicate that it may be safe to consider oral therapy with sildenafil for patients with confirmed pulmonary hypertension irrespective of the results of invasive reversibility studies. In a fast-changing world in the management of pulmonary hypertension and with the availability of new oral forms

Table 2 Haemodynamic data: catheter and echocardiographic measurements at baseline and after 3 months treatment with sildenafil

	Baseline	At 3 months	*p* Value
Catheter data			
Aorta pressure (mmHg)	125.3 ± 8.6	119.4 ± 7.6	$p = 0.071$
Systolic PAP (mmHg)	87.3 ± 5.2	73.3 ± 6.7	$p = 0.019$*
Mean PAP (mmHg)	55.8 ± 5.9	50.4 ± 6.1	$p = 0.038$
RAP (mmHg)	5.1 ± 0.9	5.9 ± 1.1	$p = 0.062$
Cardiac output (l/min)	4.7 ± 0.3	5.0 ± 0.4	$p = 0.15$
PVR (Wood units)	10.1 ± 1.7	8.6 ± 1.5	$p = 0.0091$*
PVRI (Wood units m^2)	19.1 ± 3.3	16.4 ± 3.1	$p = 0.0078$*
SVR (Wood units)	18.2 ± 1.3	17.3 ± 1.4	$p = 0.083$
PVR/SVR	0.54 ± 0.27	0.52 ± 0.30	$p = 0.087$
PA sat. (%)	65 ± 4	69 ± 3	$p = 0.037$*
Arterial sat. (%)	92 ± 1	95 ± 1	$p = 0.37$
Echocardiographic data			
RVDd (cm)	3.9 ± 0.9	3.6 ± 1.0	$p = 0.088$
IVRT (ms)	64 ± 13	70 ± 14	$p = 0.072$
TRPG (mmHg)	78 ± 17	77 ± 22	$p = 0.71$
TV inflow time (ms)	343 ± 92	374 ± 123	$p = 0.063$
TR time (ms)	487 ± 61	478 ± 93	$p = 0.094$
Vao (m/s)	1.1 ± 0.2	1.2 ± 0.4	$p = 0.32$
AoEt (ms)	270 ± 31	272 ± 25	$p = 0.61$
VmaxPA (m/s)	0.8 ± 0.2	0.9 ± 0.2	$p = 0.22$
PAAcT (ms)	64 ± 19	84 ± 25	$p = 0.032$*
PAET (ms)	227 ± 38	240 ± 39	$p = 0.081$
LV long axis (cm)	1.5 ± 0.3	1.7 ± 0.4	$p = 0.092$
Septal long axis (cm)	1.0 ± 0.3	1.4 ± 0.2	$p = 0.063$
RV long axis (cm)	1.7 ± 0.5	2.0 ± 0.5	$p = 0.071$

PAP, mean pulmonary artery pressure; RAP, right atrial pressure; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; SVR, systemic vascular resistance; RVDd, Right ventricular diastolic dimension; IVRT, isovolumic relaxation time; TRPG, tricuspid regurgitation pressure gradient; TV inflow time, tricuspid velocity inflow time; TR time, tricuspid regurgitation time; Vao, maximum velocity across aortic valve; AoET, aortic ejection time; VmaxPA, maximum pulmonary artery velocity; PAAct, pulmonary artery acceleration time; PAET, pulmonary artery ejection time; LV, left ventricle; RV, right ventricle.

*$p \leqslant 0.05$.

of therapy, the role of routine haemodynamic assessment (including acute response to vasodilators) needs to be reassessed and its indications redefined.[20]

There were no deaths during the study. Furthermore, the only patient awaiting lung transplantation was removed from the active list because of his dramatic response. Oral sildenafil was well tolerated at a dose of 50 mg t.d.s. with the exception of one patient, in which sildenafil was discontinued for a transient visual disturbance. Seven of the nine remaining patients had a marked improvement in their functional class whereas the remaining two patients remained stable with no symptomatic deterioration during the study. Furthermore, there was a significant improvement in the 6-minute walk test at 3 months. It appears that a dose of 50 mg t.d.s. is adequate for treating pulmonary hypertension and certainly current data would not support the use of the high dosage regimes previously employed.[7]

Our invasive haemodynamic data showed a significant decrease in PAP, PVR, and PVRI at 3 months along with significant changes in Doppler PAAct measurements, suggesting improved PA compliance.[21,22] There were further trends towards improved RV and LV function, as assessed by transthoracic echocardiography, albeit not significant. It may be that a longer period of therapy and a larger patient cohort are required before significant ventricular remodelling can be demonstrated with echocardiography. Furthermore, there was a significant increase in pulmonary artery oxygen saturation, with a trend towards an increase in systemic oxygen saturations. An acute haemodynamic study by Ghofrani et al.[23] in patients with severe lung fibrosis and secondary pulmonary hypertension demonstrated that sildenafil acts as a selective pulmonary vasodilator and leads to improved gas exchange by recruiting selectively well-ventilated areas of the lung. We did not specifically measure gas exchange in our patients. Hence, it remains speculative whether the increased oxygen saturations observed in our study reflected improved lung ventilation/perfusion matching, improved CO, and a reduction in right-to-left cardiac shunting in isolation or, more likely, in combination.

Limitations

We conducted an open-label, non-randomised study with invasive haemodynamic assessment, hence there is no control placebo group. The small number of patients studied, due to the rarity of the disease, yields statistical testing with a low power and because of the multiplicity

of tests, we are aware that both false negative and false positive results cannot be excluded. We considered it unethical to submit patients to further vasodilator testing with agents other than intravenous sildenafil, as per our protocol calling for intention-to-treat with oral sildenafil irrespective of acute vasodilator response. Further studies with a larger group of patients are required and are underway to shed more light on the relative response to sildenafil according to baseline NYHA class and the influence of concurrent medication.[24]

Conclusions

Sildenafil therapy, both in its intravenous and oral form, is well tolerated and appears to be safe in patients with pulmonary hypertension. Mid-term oral sildenafil therapy led to improved pulmonary haemodynamics and improved functional class and exercise tolerance. Sildenafil may, therefore, have a role in the treatment of patients with pulmonary hypertension. Additional studies with sildenafil are warranted to assess its long-term effects and the role of combination therapy with prostanoids and endothelin antagonists.[24]

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