Efficacy and Safety of High Dose Generic Sildenafil in Thai Patients with Pulmonary Arterial Hypertension

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Objective: *Sildenafil, an orally administered phosphodiesterase type 5 (PDE-5) inhibitor, was known for enhancing the downstream effects of NO. It was approved for treatment in patients with pulmonary arterial hypertension (PAH). Recently, a generic sildenafil (Unison Laboratories, Thailand) was proved to have the same bioequivalent as in the original formula. The authors conducted a 12-week case series to study the efficacy and safety of Elonza® (generic sildenafil) in PAH patients.*

Material and Method: *Comparison of both hemodynamic data from cardiac catheterization and clinical outcome such as six minute walk test (6MWT) were performed to assess the efficacy of generic sildenafil at the dosage of 50 mg given orally three times daily in patients with PAH over a 12 weeks period.*

Results: *There were 20 patients whose average age was 31.4 $\pm$ 14.3 years old (13-58) and their average weight was 48.1 $\pm$ 11.9 kg (31-79). There were three idiopathic pulmonary artery hypertensions (IPAH) and 17 congenital left to right shunts. There was a 15.1% decrease in pulmonary vascular resistance index (PVRi) from 20.5 $\pm$ 13.9 to 17.4 $\pm$ 2.9 Wood unit m^2 at the end of 12 weeks ($p = 0.044$). The ratio of pulmonary to systemic vascular resistance (PVR/SVR) was also decreased from 0.71 $\pm$ 0.57 to 0.52 $\pm$ 0.41 ($p = 0.014$). 6MWT increased significantly from 271 $\pm$ 59 meters (m) at baseline to 297 $\pm$ 48 m, 307 $\pm$ 43 m and 321 $\pm$ 52 m at week 2, 6 and 12, respectively ($p = 0.01$). There was no significant change in other hemodynamic parameter, Borg dyspnea score, and functional class.*

Conclusion: *At the end of the 12-week treatment, a 50 mg three times daily of generic sildenafil given to patients with PAH was shown to have benefit on decreasing PVRi, PVR/SVR ratio. There was also an increase in mean average of 6MWT at the end of 12 weeks.*

Keywords: *Sildenafil in pulmonary arterial hypertension*

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Pulmonary hypertension (PH) is a life-threatening disease characterized by increasing in pulmonary artery pressure from progressive pulmonary vasoconstriction, thrombosis or remodeling of the pulmonary vasculature[1,2]. The subgroup of PH known as pulmonary arterial hypertension (PAH) was defined by the fourth World Symposium on Pulmonary Hypertension[3-5] as a resting mean pulmonary arterial pressure (mPAP) $\geq$ 25 mmHg with normal left ventricular function defined by pulmonary arterial wedge pressure $\leq$ 15 mmHg. The new definition has also included pulmonary vascular resistance (PVR) that must be $\geq$ 3 Wood units. The recognition that PAH progression was characterized by vascular remodeling and an imbalance between proliferative and anti-inflammatory mediators led to the identification of the importance of three pathways for treatment of PAH which are endothelin, prostacyclin, and nitric oxide (NO). Treatment with these PAH-specific drugs has evolved dramatically over the past 15 years.

In Thailand, beraprost sodium (BPS), an oral prostacyclin, is the only PAH-specific drug in the national essential drug list. At high dosage, this oral prostacyclin was shown to have a comparable acute hemodynamic effect as good as inhaled nitric oxide[6]. Galie[7] reported an improvement of six minutes walk test (6MWT) in WHO functional class II or III PAH patients using BPS. This improvement occurred during early phases of treatment but attenuated with time[7,8]. Sildenafil, an orally administered a phosphodiesterase type 5 (PDE-5) inhibitor, was known for enhancing the downstream effects of NO mediated vasodilator.

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Sildenafil Use in Pulmonary Hypertension (SUPER) trial[9] has led to the approval of sildenafil for the treatment of pulmonary arterial hypertension by the Food and Drug Administration (USA) in 2005 and its European counterpart, the European Medicines Agency.

Recently, a generic sildenafil (Rakshit Drugs PVT. LTD., Hyderabad, India and Unison Laboratories, Thailand) was locally produced at lower price. The medicine (formally known as Erec-50) is now registered as Elonza®. A comparison of this product to Viagra® (Pfizer, Australia)[10] showed that its maximal plasma concentration (C_{max}) and area under the plasma concentration versus time curve ($AUC_{0\text{-}t\ last}$) are within the Food and Drug Administration Guideline range of bioequivalence (0.80 to 1.25).

Material and Method

The authors conducted a non-randomized and non-placebo-controlled prospective trial in the presented patients. The objectives were to study the efficacy and safety of generic sildenafil (Elonza®) at the dosage of 50 mg given orally three times daily in PAH patients for 12 weeks. The authors compared both the hemodynamic and clinical data such as six minutes walk test (6MWT). The present study was approved by Siriraj Ethics Committee, Mahidol University. Informed written consent was taken before inclusion in the present study from all the participants. The present study was supported by a Grant from Medline Co., Ltd (Thailand).

Patients selection

Twenty patients were recruited if they had PAH according to the established criteria and classification[11-13]. The inclusion criteria were 1) Male or female with their age older than 12 years old, 2) Patients must be in functional class II or more (1988 WHO functional classification), 3) All patients will undergo a complete cardiac catheterization. PAH was defined by resting mean pulmonary arterial pressure (mPAP) $\geq$ 25 mmHg and pulmonary arterial wedge pressure $\leq$ 15 mmHg. Measurement of cardiac output was performed using standard Fick principle (assumed oxygen consumption). Then calculated pulmonary vascular resistance (PVR) was obtained. PAH defined by calculated PVR was more than 3 Wood-unit, 4) 6 MWTs was greater than 100 m or less than 450 m, 5) Their clinical status has to be stable three months before enrollment, 6) Patients must be PDE 5 inhibitor naive in the last three months, and 7) The female patient was infertile or should have birth control by using a device. The exclusion criteria were, 1) Resting systolic blood pressure < 80 mmHg, 2) Ejection fraction measured by echocardiography < 40%, and 3) Patients who were known to have a plan of undergoing major surgery in the next three months.

Clinical evaluation was conducted by physical examination. Cardiac catheterization was performed at the start of the present study and at 12 weeks. Baseline transcutaneous oxygen saturation, 6 MWTs, Borg Dyspnea score, WHO functional class were measured at the start of the present study, after 2, 6, and 12 weeks.

Drug and dosage

All patients received Elonza® with a starting dose of 25 mg three times daily for 1 week and maintained at 50 mg three times daily for 11 weeks.

Outcome measure

The primary endpoint of the efficacy was the reduction of pulmonary vascular resistance index (PVRi) from the baseline to week 12. The secondary endpoint included all other hemodynamic parameters (mPAP = mean pulmonary artery pressure, mAO = mean aortic pressure, Aosat = aortic oxygen saturation, Qp: Qs = ratio of pulmonary blood flow to systemic blood flow, PVR/SVR = ratio of pulmonary vascular resistance to systemic vascular resistance) and clinical outcome such as WHO functional class, 6 minute walk test (6MWT), Borg Dyspnea score (post six minute walk test).

Statistical analysis

The primary outcome of pulmonary vascular resistance index (PVRi) from the baseline to week 12 was compared with paired t-test. Other parameters were compared at baseline, and at week 2, 6 and 12 using repeated ANOVA. The change in WHO functional class was compared using Wilcoxon Signed Rank Test. A p-value of less than 0.05 was considered statistically significant difference. All statistical analysis was performed using SPSS program version 17.

Results

Twenty patients were enrolled, including seven males and 13 females. Their average age was 31.4 $\pm$ 14.3 years old (13-58) and their average weight was 48.1 $\pm$ 11.9 kg (31-79). Their diagnoses were IPAH (3), atrial septal defect (ASD) (7), ventricular septal defect (VSD) (5), patent ductus arteriosus (1), Truncus

Table 1. Hemodynamic data from cardiac catheterization performed at baseline and at week 12 (n = 19)

Hemodynamic	Baseline	Week 12	p-value
mPAP (mmHg)	65.7 ± 20.1	64.2 ± 20.6	0.304
mAO (mmHg)	87.1 ± 13.4	90.9 ± 11.8	0.283
Aosat (%)	90.8 ± 7.8	92.1 ± 7.9	0.155
Qp: Qs	1.35 ± 0.9	1.54 ± 0.8	0.543
PVRi (Wood unit m^2)	20.5 ± 13.9	17.4 ± 2.9	0.040
PVR/SVR	0.71 ± 0.57	0.52 ± 0.41	0.014

mPAP = mean pulmonary artery pressure; mAO = mean aortic pressure; Aosat = aortic oxygen saturation, Qp:Qs = ratio of pulmonary blood flow to systemic blood flow; PVRi = pulmonary arteriolar resistance index to body surface area (Wood unit m^2); PVR/SVR = ratio of pulmonary vascular resistance to systemic vascular resistance)

arteriosus (3) and aortopulmonary window (1). All patients tolerated well to the recommended dosage for 12 weeks. The average dosage of sildenafil was 3.11 mg/kg/day. One patient (a 17-year-old girl with large ASD) died suddenly from acute hemoptysis at week 11. No available data on hemodynamic parameter was obtained in this patient. Only 19 patients had completed cardiac catheterization at week 12. The hemodynamic data from cardiac catheterization were performed at baseline and at week 12 are shown in Table 1.

Hemodynamic data at baseline and at 12 weeks

There was no significant change in mPAP, mAO, Aosat and Qp: Qs at baseline and at week 12. The PVRi decreased from 20.5 ± 13.9 to 17.4 ± 2.9 Wood unit m^2 at the end of 12 weeks ($p < 0.04$). The mean decreased in PVRi at week 12 is 3 Wood unit m^2 (95% confidence interval of 0.09 to 6.15). This represented an average of 15.1%. The ratio of PVR/SVR was also decreased from 0.71 ± 0.57 to 0.52 ± 0.41 ($p = 0.014$).

Comparison of 6MWT, Borg Dyspnea score and functional class at baseline and at week 2, 6, and 12

Six minute walk test increased significantly from 271 ± 59 meters (m) at baseline to 297 ± 48 m, 307 ± 43 m and 321 ± 52 m at week 2, 6 and 12, respectively ($p = 0.01$). The mean increased in 6MWT at week 2, 6 and 12 were 25.8 ± 5.4 m, 35.6 ± 52.7 m, 50.3 ± 53.3 m ($p = 0.01$). The average value of Borg dyspnea score from baseline to week 2, 6 and 12 were 3.2 ± 2.4, 3.1 ± 2.5, 4.0 ± 2.1 and 3.7 ± 1.9 respectively. However, this change was not statistically significant ($p = 0.188$). Changes in 6MWT and Borg Dyspnea score are shown in Fig. 1. The proportion of functional class from at week 2, 6, and 12 are also shown in Fig. 2. There was a trend toward improving in functional class from baseline to 12 weeks, however, this was not statistically significant ($p = 0.059$).

Adverse reactions

All of the patients tolerated sildenafil as their monotherapy for a 12-week period. No significant side effects were reported during the study period.

Discussion

The rationale for the use of phosphodiesterase type 5 inhibitors in pulmonary arterial hypertension is augmentation of the cyclic guanosine monophosphate

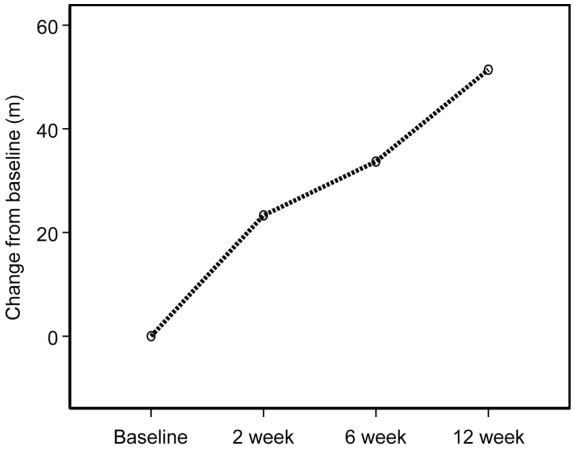

Fig. 1 Changes of 6-minute walking distance in meters (m) were shown from baseline, at 2 week (wk), 4 wk and 12 wk

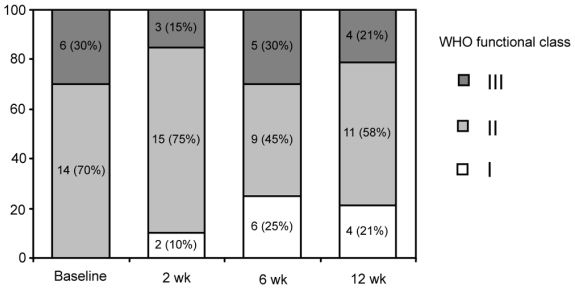

Fig. 2 The proportion of WHO functional class from at 2 weeks (wk), 6 wk and 12 wk are shown here (one patient died at week 11)

pathway. By inhibiting the hydrolysis of cyclic guanosine monophosphate, the authors can consider sildenafil as an intracellular nitric oxide producer. Agents in this class have several effects such as vasodilatory, antiproliferative, and proapoptotic that may reverse pulmonary artery remodeling[4,14-16]. Sildenafil is a preferential inhibitor of phosphodiesterase type 5 used in Thailand.

Since the SUPER trial, sildenafil was approved by US FDA for treatment of PAH. It was also recommended in the new updated evidence-based treatment algorithm in PAH in 2009[17]. However, the optimal dose of sildenafil for PAH remains unknown. In USA, sildenafil dosage recommendation was restricted to 20 mg three times daily as in Revatio®[18]. Although, all doses given in SUPER trial[9] (20 mg, 40 mg and 80 mg) three times daily had similar effects with regard to 6MWT results. There was a trend toward improved hemodynamics with increasing doses of sildenafil. A higher daily dosage of sildenafil up to 500 mg has been reported[19]. A target dose of 150 mg/day appears to be optimal[20] with favorable effect on hemodynamic and 6MWT. The authors then decided to use sildenafil 50 mg three times daily, which is easily available as a 50 mg tablet of locally manufactured formulation.

The previous test for pharmacokinetic study showed 90% confidence interval of the mean proportion of Ln AUC0-t last and Ln Cmax are within the acceptable range of 0.80-1.25 according to the Thai FDA guideline[10]. This indicates that generic sildenafil, Elonza®, was bioequivalent to the Reference formulation (Viagra®, Pfizer Pty Limited, Australia) in terms of both rate and extent of absorption.

The presented patients showed that from baseline to the end of 12 weeks the PVRi decreased from 20.5 $\pm$ 13.9 to 17.4 $\pm$ 2.9 1Wood unit m^2. The average decrease in PVRi was 3.1 Wood unit m^2 (95% confidence interval of 0.09 to 6.15; $p = 0.044$). In SUPER trial the PVR at base line and at the end of 12 weeks for different dosages of sildenafil 20 mg, 40 mg, 80 mg three times daily as follows (Wood unit) 13.1 $\pm$ 6.4, 12.3 $\pm$ 5.8, 10.9 $\pm$ 5.5 and 11.5 $\pm$ 7.5. The baseline PVR from the present study appeared higher than in the SUPER trial. However, both trials showed an improvement in PVR after treatment of 12 weeks. The fact that there was no significant change in mPAP in the present study may be due to the majority of the present patients being uncorrected congenital heart disease, which led to high pulmonary artery pressure and persisting left to right shunt.

In SUPER trial[9], the mean placebo-corrected treatment effects of 6 MWT among 266 patients at week 12 were 45 meters among those receiving 20 mg of sildenafil (99% confidence interval, 21 to 70; $p < 0.001$), 46 meters for those receiving 40 mg (99 percent confidence interval, 20 to 72; $p < 0.001$) and 50 meters for those receiving 80 mg (99 percent confidence interval, 23 to 77; $p < 0.001$). The present study showed that the mean increase in 6MWT from baseline to 12 wk was 50.3 $\pm$ 53.3 meters ($p = 0.01$). The authors found that with the regimen of 50 mg of sildenafil given three times daily had a comparable treatment effect measured by 6MWT to the original formula. This dosage can be considered higher than usual 20 mg three times daily dose that was recommended[9]. In fact in the extension study from SUPER trial, all patients were treated with 80 mg three times daily if tolerated[19]. The authors in the trial had concluded that "based on these data, 20 mg three times daily appears to be a reasonable initial dose; an increase to 40 mg three times daily, 80 mg three times daily, or both may be considered in order to achieve or maintain favorable effects". They also recognize that limited data are currently available regarding the optimal dose of sildenafil for long-term treatment and that the use of higher doses may be hampered by the restricted approval in USA. In addition, a study of 30 patients the effect high dosage of sildenafil up to 50 mg plus iloprost was more potent than 12.5 mg of sildenafil plus iloprost[21]. Hence, there are more convincing evidences of favorable outcome in higher dosage of sildenafil. It underscores the importance of locally made sildenafil with a more affordable price.

Conclusion

Oral sildenafil in locally made formula (Elonza®) is an effective and safe drug for treatment of patients with PAH. The present study showed that sildenafil at high dosage of 50 mg three times daily has a treatment effect (on PVRi and 6 MWT) at the end of 12 weeks. This benefit was comparable to the original formula. These formulas (50 mg, 100 mg of sildenafil citrate) are also convenient to administrate in anticipating a higher dosage of sildenafil will be needed for long-term treatment.

Potential conflicts of interest

None.

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ประสิทธิภาพของการใช้ยาในประเทศ sildenafil ขนาดสูงในผู้ป่วยไทยที่มีภาวะความดันหลอดเลือดแดงปอดสูง

กฤตย์วิกรม ดุรงค์พิศิษฏ์กุล, สุวรรณา พรรัตนรังสี, พรทิพย์ ปัญจสมานวงศ์, ปวีณา จิงสมประสงค์

วัตถุประสงค์: *ยา sildenafil เป็นยารับประทานที่ออกฤทธิ์โดยยับยั้งเอนไซม์ phosphodiesterase ซึ่งทำให้เพิ่มผลของ NO และได้รับการอนุมัติให้ใช้ในผู้ป่วยที่มีภาวะความดันหลอดเลือดแดงปอดสูง โดยปัจจุบันมีการผลิตยานี้ในประเทศ (Unison Laboratories) จากการศึกษาพบว่ามีค่าชีวสมมูลของยานี้เหมือนกับยาต้นตำรับ จึงทำการศึกษาเพื่อดูผลการรักษาและความปลอดภัยในการใช้ยา elonza® ในผู้ป่วยกลุ่มนี้*

วัสดุและวิธีการ: *ค่า Hemodynamic จากการตรวจสวนหัวใจ และผลการตรวจทางคลินิกในผู้ป่วยเช่นระยะทางของการเดินในระยะเวลา 6 นาที ถูกวัดเปรียบเทียบในผู้ป่วยที่มีภาวะความดันหลอดเลือดแดงปอดสูงที่ได้รับยาในประเทศ sildenafil ขนาด 50 มก. วันละ 3 ครั้ง ระหว่างค่าพื้นฐานและที่ระยะเวลา 12 สัปดาห์*

ผลการศึกษา: *มีผู้ป่วยจำนวนทั้งสิ้น 20 ราย อายุเฉลี่ย 31.4 ± 14.3 ปี (13-58) และมีน้ำหนักเฉลี่ย 48.1 ± 11.9 กิโลกรัม (31-79) ผู้ป่วย 3 ราย ได้รับการวินิจฉัยว่ามีภาวะความดันหลอดเลือดแดงปอดสูงชนิดไม่ทราบสาเหตุ และ 17 ราย เป็นโรคหัวใจพิการแต่กำเนิด พบว่าค่าดัชนีความต้านหลอดเลือดแดงในปอดลดลงร้อยละ 15.1 จาก 20.5 ± 13.9 Wood unit m^2 เป็น 17.4 ± 2.9 Wood unit m^2 ที่ระยะเวลา 12 สัปดาห์ (p = 0.04) สัดส่วนของค่าความต้านหลอดเลือดในปอดเทียบกับหลอดเลือดร่างกายลดลงจาก 0.71 ± 0.57 เป็น 0.52 ± 0.411 (p = 0.014) ระยะทางของการเดินในระยะเวลา 6 นาที เพิ่มจาก 271 ± 59 เมตร (ม.) ที่เริ่มต้นเป็น 297 ± 48 ม., 307 ± 43 ม. และ 321 ± 52 ม. ที่สัปดาห์ที่ 2, สัปดาห์ที่ 6 และสัปดาห์ที่ 12 ตามลำดับ (p = 0.01). ไม่พบการเปลี่ยนแปลงในการวัดค่า hemodynamic อื่นหรือ ค่า Borg dyspnea index หรือ functional class*

สรุป: *ผู้ป่วยที่มีภาวะความดันหลอดเลือดแดงปอดสูงที่ได้รับยาในประเทศ sildenafil ขนาด 50 มก วันละ 3 หน เป็นระยะเวลา 12 สัปดาห์มีผลการรักษาไปในทางที่ดีขึ้นโดยพบว่า ค่าดัชนีความต้านหลอดเลือดแดงในปอด และสัดส่วนของค่าความต้านหลอดเลือดในปอด เทียบกับหลอดเลือดร่างกายจากการตรวจสวนหัวใจลดลง และค่าเฉลี่ยของระยะทางของการเดินในระยะเวลา 6 นาที เพิ่มขึ้นที่ 12 สัปดาห์*