The Use of Bosentan in Pulmonary Arterial Hypertension

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Abstract. The main class of drugs specific treatment for pulmonary arterial hypertension (PAH) were calcium channel blocker, sildenafil, bosentan, beraprost and iloprost. Bosentan is a competitive, specific dual receptor (ET-A and ET-B) antagonist. The aim of this study was to investigate the pattern, reason, effect, and adverse drug reaction of bosentan in PAH patients at Queen Sirikit Heart Center of the Northeast, Thailand. A retrospective study had been collected the data from medical record and electronic database for 3 years. The results showed from the 16 patients with PAH, 7 patients concluded in the criteria, but only medical record of 5 patients could be accessed. The 4 patients (80%) used in monotherapy and 1 patient (20%) in combination with sildenafil. The reason for prescribing, 3 patients (60%) failed to use sildenafil for more than three months and 2 patients (40%) used for first line treatment in WHO FC II. After one-year treatment, 4 patients (80%) treated with bosentan had improved WHO FC and improved 6MWD; the mean difference before and after one year was 40 m ($p = 0.157$). In addition, most patients did not have any adverse drug reaction. Most of prescription pattern of bosentan was monotherapy and used in patients who failed from sildenafil. Bosentan has been shown to improve WHO FC and 6MWD in patients with PAH.

Keywords: Bosentan 1 · pulmonary arterial hypertension 2

1 Introduction

Thailand 2012, the main class of drugs specific treatment for pulmonary arterial hypertension were calcium channel blocker, sildenafil, bosentan, beraprost and iloprost [1]. Bosentan is a competitive, specific dual receptor (ET-A and ET-B) antagonist. Type A receptors are expressed in pulmonary vascular smooth muscle cell and contribute to ET-1 induced contraction and proliferation. ET-B receptors are expressed in the endothelial cells and lead to ET-1 clearance and vasodilation. These drugs were used for WHO FC II or III patient who was not efficacy with sildenafil. Bosentan leaded to vasodilation and increase pulmonary arterial pressure [2]. It improved the Borg dyspnea index and functional class and increased the time to clinical worsening [4–6]. These were proved 6 min walk distance (6MWD) and cardiac index as mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) were decreased [7, 8]. However, the

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cost utility analysis of drug treatment for PAH in Thai context used sildenafil as the first line of treatment and this study evaluated the alternatives for both first- and second-lines treatment concluded bosentan, the combination therapy but the cost and quality adjusted life year were not significantly different and cost effective in the Thai context. This study investigated the pattern, reason, effect and adverse drug reaction of bosentan that proved the drug treatment guidelines in PAH patients at Queen Sirikit Heart Center of the Northeast.

2 Material and Method

2.1 Study Method

This study was a retrospective study, collecting data from medical and computer database from the 1 January 2013 to the 1 January 2016.

2.2 Subjects

The samples were the PAH patients, aged over 18 years old at Queen Sirikit Heart Center of the Northeast, Khon Kaen University.

2.3 Data Collection

The patient's data collecting form consist in 6 parts, 1) General characteristic: gender, age, weight, height, first of diagnosis, duration of treatment and classification of pulmonary arterial hypertension. 2) Prescription pattern 3) Clinical test: liver function test, hemodynamic test, exercise capacity and WHO functional class of the patient who received bosentan. 4) Adverse drug reactions while taking bosentan. 5) Clinical test: liver function test, hemodynamic test, exercise capacity and WHO functional class of the patient who received sildenafil. 6) Adverse drug reactions while taking sildenafil. This study collected the adverse drug reaction of sildenafil before using bosentan.

2.4 Data Analysis

Descriptive static used to analyse general information with primary end point such as classify gender, classification of PAH and WHO functional class by nominal scale were in frequency and percentage, interval, and ratio scale such as age, weight and 6-min walk distance were in mean and standard deviation. The change of WHO functional class, 6MWD, Borg dypsnea index, Cardiac index, Pulmonary vascular resistance, Pulmonary capillary wedge pressure and right atrial pressure before and after taking bosentan was compared with Paired-t test. If the data was nonparametric, Wilcoxon signed rank test was used. The statistical analysis was performed by SPSS program with p-value of less than 0.05 was considered statistically significant difference.

3 Result

3.1 Patient Characteristics

The five patients consist of 3 females (60%), 2 males (40%) and age 40.80 ± 15.88 years. Patients in WHO FC I, II and III. 3 patients that were congenital heart disease with atrial septal defect (ASD) that associated with eisenmenger symptom, and 1 patient were ventricular septal defect (VSD). These patients received bosentan 62.5 mg bid and the baseline 6MWD average 313.60 ± 107.59 m (Table 1).

3.2 Prescription Pattern of Bosentan

Bosentan was used in 4 patients in monotherapy and 1 patient in combination therapy with sildenafil. Three patients of this study used bosentan after sildenafil which could not respond for 3 months. Another 2 patients used bosentan as the first line drug therapy in WHO FC II as shown in Table 2.

Table 1. Baseline characteristic of the patients

Patient's Data	n (%)
Sex	
Male	3(60)
Female	2 (40)
age — year	
mean ± sd	46.80 ± 15.88
Age range	27–71
weight — kg	59.24
Duration of diagnosis drug exposure — year	5.64 ± 5.19
PAH classification— n (%)	
Associated with congenital heart disease	5 (100)
WHO FC — n (%)	
II	3 (60)
III	1 (20)
IV	1 (20)
6MWD — m	313.60 ± 107.59
Comorbidity — n (%)	
HTN	1 (20)
DM	1 (20)
Eisenmenger syndrome	5 (100)
ASD	3 (60)
VSD	1 (20)

Table 2. Prescription pattern bosentan and drug adjustment

Code	Prescription pattern	(%)	Does of bosentan
01	Combination with sildenafil	(20)	62.5 mg bid (does not adjust the dose)
02	monotherapy	(80)	
03			
04			
05			

Table 3. 6MWD drug effect for 1-year treatment of bosentan

code	6MWD (m) Baseline	6MWD (m) After 1 year	95% Confidence Interval	p-value
01	370.0	380.0		
02	220.0	330.0		
03	180.0	180.0		
05	368.0	448.5		
mean ± SD	313.60 ± 107.59	353.70 ± 107.51		
Difference of 6MWD (mean ± SD)	40.10 ± 51.58		−23.94 to 104.14	0.157

3.3 Clinical Effect of Bosentan

3.3.1 6MWD

Compared to baseline, mean ± sd 6MWD increased after 1 year (313.60 ± 107.59 m. and 353.70 ± 107.51 m.). This different did not reach statistical significance, increased 40.10 ± 51.58 m. (95% CI −23.94 to 104.14; p = 0.157) (Table 3).

3.3.2 WHO Functional Class

The improvement in 6MWD was consistently different from WHO FC class. The mean increases in 6 MWD comparing baseline in patient in function class II, III and IV were improved but 1 patient did not improve.

3.3.3 Adverse Drug Reaction of Bosentan

Commonly reported side effects of bosentan include headache, faintness, dizziness, coughing, dyspnea, redness of the skin, nosebleed, and hepatic insufficiency. 1 patient of this study had angina pain after excess the activity and did not identify from bosesntan treatment.

Table 4. Individual does of sildenafil and WHO FC effect

code	age (year)	Does sildenafil (mg/day) baseline	Does sildenafil (mg/day) exposure	sildenafil drug duration (month)	Duration sildenafil drug adjustment (month)	Baseline WHO FC	After 1 year WHO FC
1	42	25	25	27	no	I	I
02	49	25	50	34	4	I	II
04	27	25	75	10	5	II	III
			mean	23.67	4.5		

3.4 Clinical Effect of Sildenafil

Three out of 5 patients switched to bosentan after receiving sildenafil, first dose of drug was 25 mg per day. Two patients were adjusted to the new dose at 25 mg bid and 25 mg three time a day (Table 4).

3.4.1 6MWD

A patient out of 3 patients in sildenafil treatment has increased the 6MWD test, baseline was 260 m and after treat was 202 m.

3.4.2 WHO Functional Class

The improvement in 6MWD was consistently different WHO FC class. The mean increases in 6 MWD compared based line in patient in function class II was improved but 2 patients did not improve.

3.4.3 Adverse Drug Reaction of Sildenafil

Commonly reported side effects of sildenafil include headache, faintness, dizziness, coughing, redness of the skin, diarrhea, nosebleed, fever, influenza, muscle, and skeleton pain. 1 patient of this study had a headache and fatigue.

4 Discussion

This study investigated the pattern, drug adjusted, adverse drug reaction of bosentan and sildenafil in PAH patients aged over 18 years old at Queen Sirikit Heart Center of the Northeast, Khon Kaen University. Sixteen patients received bosentan and 7 patients were included in this study. The exclusion were 18 patients with 1 patient aged less than 18 years old, 9 patients could not collect the data and 8 patients used bosentan for less than 3 months. The subject were 5 patients of PAH who received sildenafil before were 3 patients. The data was collected from PAH related Eisenmenger's syndrome patient

and associated congenital heart disease. Dose of drug was 62.5 mg bid. 313.60 ± 107.59 was mean of baseline 6MWD and WHO FC in I, II and III.

Bosentan was the first oral therapy for PAH and effected on exercise capacity and cardiopulmonary hemodynamic. These increase the distance of 6MWD, mean pulmonary artery pressure (mPAP) but decrease pulmonary vascular resistance (PVR) [7, 8]. 6MWD evaluated exercise capacity and WHO FC class that was the assessment the mortality of PAH such as the prognosis disease. There are concerns that the 6MWD is affected by number of factors other than pulmonary hypertension, including age, gender, height, weight and musculo-skeletal condition. The hemodynamic hallmarks of PAH include a pulmonary venous pressure, mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistant (PVR) that were evaluated by echocardiography as noninvasive procedure or RHC as invasive procedure. Noninvasive assessment is the assessment to evaluate hemodynamic and no evidence for RHC evaluated in PAH [3, 13–15]. This study only assessed the effect of bosentan and sildenafil treatment.

The heart association of Thailand PAH guideline in 2013 suggested bosentan was the treatment drug for PAH in WHO FC II or III that did not respond to sildenafil treatment or WHO FC class IV [1]. ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension in 2015, bosentan used for monotherapy with PAH in WHO FC II, III and IV [3]. 80% of bosentan drug prescription were monotherapy and 60% were bosentan after did not response with sildenafil more than 3 months. The average adjustment of bosentan from sildenafil was 2 years.

BREATHE-1 evaluated bosentan 62.5 mg bid for four weeks then target dose as 125 mg or 250 mg bid for a minimum 16 weeks. After 16 weeks of 125 mg or 250 mg bid, bosentan improved the 6MWD by 36 m [6]. Bosentan 62.5 mg bid for 12 weeks did not evaluate in 3 to 6 months of the treatment and did not follow up the treatment in the last observation carried forward (LOCF) at 12 months of treatment. Bosentan improved 80% of WHO FC increased and 40 m for 6MWD in PAH. The difference of 6MWD was significantly in the treatment. The results were different because the subject in the past studies had IPAH, but this study had PAH occurring in association with congenital heart disease that related with Eisenmenger's syndrome. The clinical research founded that 60% of sildenafil treatment changed to bosentan by worsening treatment, dose of drug was 25 mg per day. Thailand 2013 founded WHO FC decrease 2 patients (66.7%) even adjusted sildenafil to 50 mg and 75 mg per day before receiving bosentan. The maximum doses for PAH in Thailand are 60 mg per day but if the patients do not respond, could receive the maximum dose at 240 mg per day [16, 17]. Even the WHO FC class improved by sildenafil but effect adverse of drug was decrease in ages patient from NO. Sildenafil inhibit enzyme phosphodiesterase type 5 (PDE-5) which inactivate cGMP to GMP. cGMP decreased was the sildenafil precaution in ages PAH patient. The age and drug responses were not obviously different and 6MWD did not analyze from the database.

Adverse drug reaction of this study from the objective data, did not evaluate with the specialist. Bosentan in this study did not occur adverse drug reaction and did not find hepatic insufficiency, sildenafil found adverse drug reaction such as headache.

Sample size was the limitation of this study by health care scheme in Thailand, bosentan did not contain for PAH patient in Thai context. These were not significant

differences in WHO FC and 6MWD. Further studies are necessary to determine the evaluate of data duration, hemodynamic by echocardiography and hepatic enzyme test in baseline and after 3 to 6 months or worse of case. WHO FC and 6MWD could evaluate in 3 to 6 months after patient received bosentan.

Bosentan was not a cost-effective for the front-line therapy such as sildenafil and other endothelin receptor antagonists but bosentan appears to be a more cost-effective alternative therapy compared with epoprostenol and conventional or palliative therapy [18–20].

5 Conclusion

This retrospective study of bosentan treatment of PAH patient aged over 18 years old at Queen Sirikit Heart Center of the Northeast, Khon Kaen University found that 4 patients received bosentan in monotherapy, a patient in combination treatment with sildenafil after 3 months worsening symptom. These were not significant differences in WHO FC and 6MWD ($p = 0.157$). Adverse drug reaction was headache from sildenafil treatment case.

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