A Retrospective Study of Bosentan in Pulmonary Arterial Hypertension Associated with Congenital Heart Disease

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Background: *Pulmonary Arterial Hypertension (PAH) plays a significant role in morbidity and mortality of patients with congenital heart disease (CHD). Bosentan, a dual endothelin receptor antagonist has been approved for PAH patients with Eisenmenger physiology (EP). The authors retrospectively reviewed the efficacy and safety of bosentan in Thai PAH patients associated with CHD.*
Material and Method: *The study population was obtained from the databases of the CHD patients at Siriraj Hospital from October 2004 to April 2007 who received 6 months of bosentan treatment. Inclusion criteria are: CHD with Eisenmenger physiology (EP) or those with severe PAH after surgical repair or interventional cardiac catheterization. Clinical characteristics including the 6 – minute walk test (6MWT) distances, oxygen saturation (O_2 sat), New York Heart Association (NYHA) functional class, and right ventricular systolic pressure (RVSP) at baseline were compared with those at 1, 3, and 6 months post bosentan treatment. Signs and symptoms of adverse events were also recorded.*
Results: *There were 11 patients from among those who fitted the inclusion criteria and whose records were examined. Their average age was 51.1 $\pm$ 10.1 years old (13-61 years old). Patients were divided into 2 groups; Group A (6 patients) was PAH with EP and Group B (5 patients) was PAH post intervention. In group A, the 6MWT increased from 151 $\pm$ 69 meters to 293 $\pm$ 61 meters ($p = 0.001$) with the average increase of 38 $\pm$ 61 meters. The O_2 sat increased from 83 $\pm$ 12.7% to 91.8 $\pm$ 5.6% ($p = 0.038$) with an average increase of 1.4 $\pm$ 0.07%. There was no significant change in right ventricular systolic pressure (RVSP). In group B, there was a trend in 6MWT improvement from 274 $\pm$ 69 meters to 312 $\pm$ 38 meters but this was not statistically different. There were improvements in the NYHA functional class in both groups. There was no significant increase in serum aminotransferase at the end of 6 months in each patient.*
Conclusion: *There are benefits of bosentan for treatment of severe PAH in CHD, especially in patients with Eisenmenger physiology. Obvious benefits are an improvement of 6MWT and O_2 sat.*

Keywords: *Pulmonary arterial hypertension, Congenital heart disease, Bosentan*

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Pulmonary Arterial Hypertension (PAH) is the crucial problem in patients with congenital heart disease (CHD)[1-2]. The authors' database at Siriraj Hospital has shown that the number of PAH associated with CHD tend to be increasing every year. From 2004 to 2006, the annual percentage of the admitted patients who were diagnosed with PAH in CHD increased from 13% to 14% and 22% respectively. Compared to studies in European countries, there is only 10-15% of PAH associated with CHD[12].

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Previously, the authors reported the effect of 12 months combination therapy of oral beraprost and twice daily inhaled iloprost in 23 CHD patients with severe PAH[3]. There were 12 patients who had PAH post cardiac catheterization interventional procedure and 11 patients with Eisenmenger physiology (EP). There was a significant improvement of 6MWT from an average of 268 ± 70 meters to 308 ± 57 meters at the end of 12 months. However, there was no significant difference in oxygen saturation. It appeared that there was some limitation, primarily due to side effects, regarding using combination therapy (beraprost or iloprost). In 2003, Barst reported an improvement of 6MWT in PAH patients using beraprost. The improvement in 6MWT occurring during early phases of treatment in WHO functional class II or III patients, but this effect attenuated with time[4]. The effect of beraprost appeared to be effective in the short term, but not over time in patients with WHO functional class II or III[4,5].

Another well-known drug proven effective in managing PAH is the endothelin receptor antagonist (ERA)[6]. Bosentan, one of the endothelin receptor antagonists available in Thailand, has been shown to improve exercise tolerance, hemodynamics, survival and quality of life in patients with idiopathic pulmonary hypertension (IPAH) and that PAH associated with a connective tissue disease (CTD). All patients have good tolerability with bosentan[7-10]. In the first randomized placebo controlled study in CHD with Eisenmenger physiology, BREATH-5 by Galli et al, patients showed improvement in exercise capacity and decrease in pulmonary vascular resistance over 16 weeks of the treatment period, without a worsening of oxygen saturation[11].

The authors retrospectively reviewed data of PAH patients with CHD taking bosentan at Siriraj Hospital for at least 6 months. The authors aimed to determine the efficacy and safety of bosentan in the treatment of Thai PAH patients associated with CHD.

Material and Method

Population

The study population was obtained from the databases of the patients who attended the adult congenital heart clinic at Siriraj Hospital between October 2004 and April 2007. Inclusion criteria included patients diagnosed with PAH associated with CHD, and included those that had been surgically repaired, and completed a 6MWT distance between 150 and 450 meters, and were clinically stable naive to bosentan. The exclusion criteria were the following: patients with systolic blood pressure < 85 mmHg, those with other conditions that may affect the ability to perform a 6-minute walk test, known coronary arterial disease, serum creatinine > 1.5 mg/dL, those with hemoglobin concentration £ 14g/dL, and those with serum aminotransferase (AST and/or ALT) values greater than 3 times the upper limit of normal. Also excluded were those receiving calcineurin inhibitors (e.g. cyclosporine A and tacrolimus), fluconazole or (and) glibenclamide (glyburide), those active on organ transplant lists, those with planned surgical intervention during the study period and those with known hypersensitivity to bosentan or any of the excipients.

Data collection

Both inpatient and outpatient medical records were reviewed to extract for the following: (i) General patient information: sex, age, bodyweight and height. (ii) Medical history: etiology of PAH, frequency of hospital admission. (iii) Baseline clinical characteristics: 6MWT distances, at rest O_2 sat, New York Heart Association (NYHA) functional class[12]. (iv) Prescribed information: bosentan dosage and other concomitant medications. (v) Follow-up clinical characteristics: 6MWT distances, at rest O_2 sat, NYHA functional class and (vi) Signs and symptoms of adverse events.

Definition of pulmonary arterial hypertension

PAH is defined as a mean artery pressure (mPAP) of greater than 25 mmHg at rest or greater than 30 mmHg with exercise when measured invasively, or right ventricular systolic pressure (RVSP) of greater than 50 mmHg by echocardiography (based on the measurement of the velocity of the tricuspid regurgitation jet).

Data analysis

Quantitative data are presented as mean ± SD unless specified as median in the text. Qualitative data are presented as percentage. Non-parametric comparison test: Mann-Whitney-U-Test was used to test the difference in mean between groups. The difference in mean within group was tested by Wilcoxon signed rank test. For all analyses, a two-sided P-value of less than 0.05 was considered statistically significant. SPSS version 12.0 was used for statistical analysis.

The present study was approved by the ethics committee of the Faculty of Medicine Siriraj Hospital for reviewing of all medical reports relevant to the present study.

Results

Eleven patients received bosentan as a monotherapy for 6 months during the study period. Their average age was 51.1 ± 10.1 years old (with the range from 13 years old to 61 years old). They were separated into two groups based on their native congenital heart lesion and treatment. Group A (6 patients) consisted of patients with Eisenmenger physiology, five with atrial septal defect (ASD) and one ventricular septal defect (VSD). Group B consisted of patients who had repaired congenital defect, four post transcatheter closure of ASD (all of them had ASD closure around 2 years prior to the study period), and one post VSD closure (5 years prior to the study period).

Baseline data

Group A patients with Eisenmenger physiology had less 6MWT when compared to group B patients (151.6 ± 69.1 meters vs. 274 ± 69.8 meters, p = 0.018), but they also had lower O_2 sat (83 ± 12.7% vs. 96.8 ± 1.3%, p = 0.45) and higher RVSP (90.2 ± 7.6 mmHg vs. 62.6 ± 19.8 mmHg, p = 0.03). All patients had a laboratory check, which included a liver function test (LFT) as a prerequisite to medication. Bosentan was started according to the recommendation by using 62.5 mg twice daily. Liver function tests were again repeated at 1 month and 6 months. Then bosentan was altered to 125 mg twice daily if there was no elevation in LFT at 1 month. Patients were continued on this regimen until the end of 6 months. The follow-up evaluation included 6MWT, O_2 sat and RVSP.

Follow-up data

All 11 patients were treated with bosentan for 6 months. The data on 6MWT, O_2 sat and RVSP at baseline (0 month), 1 month, 3 months and 6 months are shown in Table 1.

Comparison of 6MWT, O_2 sat and RVSP at pre-medication and at the end of 6 months

In group A, the six MWT increased from 151 ± 69 meters to 293 ± 61 meters (p = 0.001) at the end of six months, an average increase of 38 ± 61 meters. The O_2 sat increased from 83 ± 12.7% to 91.8 ± 5.6% (p = 0.038), an average increase of 1.4 ± 0.07%. There was no significant change in right ventricular systolic pressure (RVSP). In group B, there was a trend in 6MWT improvement from 274 ± 69 meters to 312 ± 38 meters but this was not statistically significant. The improvement in O_2 sat and RVSP were also not statistically significant either.

Data on NYHA Functional class

The authors used the New York Heart Association classification (NYHA) for functional class assessment as follows: class I (normal activity), Class II (dyspnea with mild exercise), Class III (dyspnea with less than normal activity) and Class IV (dyspnea at rest). The authors compared the NYHA functional class at baseline prior to the therapy with those found at the end of 6 month therapy. In group A there were six patients, one in NYHA class IV, three in class III, and two in class II. At the end of 6 months, three patients improved to class I, two to class II and only one patient remained in class III. None of them was in NYHA class IV.

In group B, three patients were in NYHA class II and two patients were in class III. At the end of 6 months, two patients remained in class II and three patients improved to Class I.

Adverse reactions

All of the patients tolerated bosentan as their

Table 1. Patients were divided into group A (Eisenmenger physiology) and group B (post repair). The data from the 6 minute walk test (6MWT), oxygen saturation (O_2 sat) were obtained at baseline (0 month), 1 month, 3 months and 6 months and right ventricular systolic pressure (RVSP) were obtained at baseline (0 month), 3 months and 6 months

	Group A (n = 6)	Group B (n = 5)
6 MWT at 0 month (meters)	151 ± 69	274 ± 69
6 MWT at 1 month (meters)	215 ± 98	310 ± 14
6 MWT at 3months (meters)	287 ± 56	314 ± 24
6 MWT at 6 months (meters)	293 ± 61	312 ± 38
O_2 sat at 0 month (%)	83.0 ± 12.7	96.8 ± 1.3
O_2 sat at 1 month (%)	87.8 ± 11.6	96.0 ± 1.8
O_2 sat at 3 months (%)	88.6 ± 11.2	97.2 ± 1.3
O_2 sat at 6 months (%)	91.8 ± 5.6	98.2 ± 0.8
RVSP at 0 month (mmHg)	90.2 ± 7.6	62.6 ± 19.8
RVSP at 3 month (mmHg)	92.0 ± 5.2	62.7 ± 17.7
RVSP at 6 month (mmHg)	92.6 ± 9.1	66.7 ± 18.5

Table 2. Liver enzymes in group of patients at baseline (0 month), 1 month, and 6 months (ALT and AST)

	0 month	1 months	6 months	p-value
AST (U/L)	23.3 ± 10.5	24.8 ± 11.1	27.4 ± 8.5	NS
ALT (U/L)	20.5 ± 12.4	18.7 ± 5.1	20.4 ± 5.2	NS

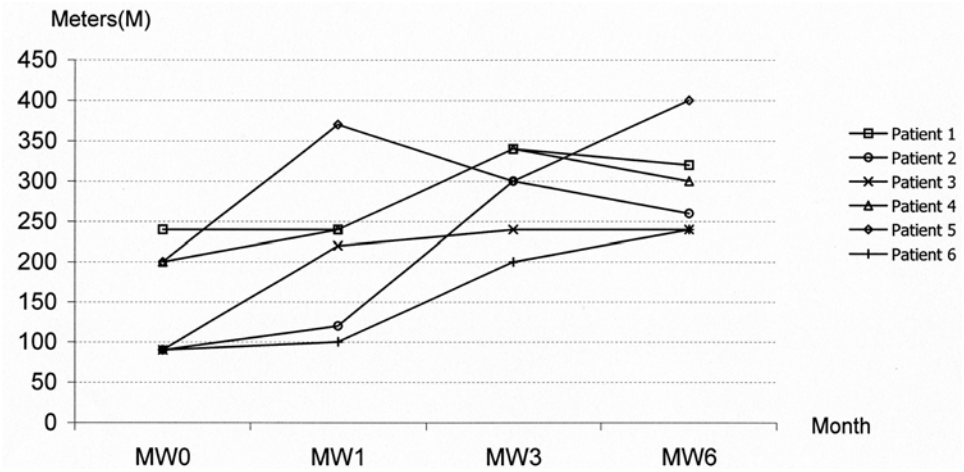

Fig. 1 6-minute walk test in group A patients (Eisenmenger Physiology: EP) at baseline (MW0), 1 month (MW1), 3 months (MW3) and 6 months (MW6), p = 0.001

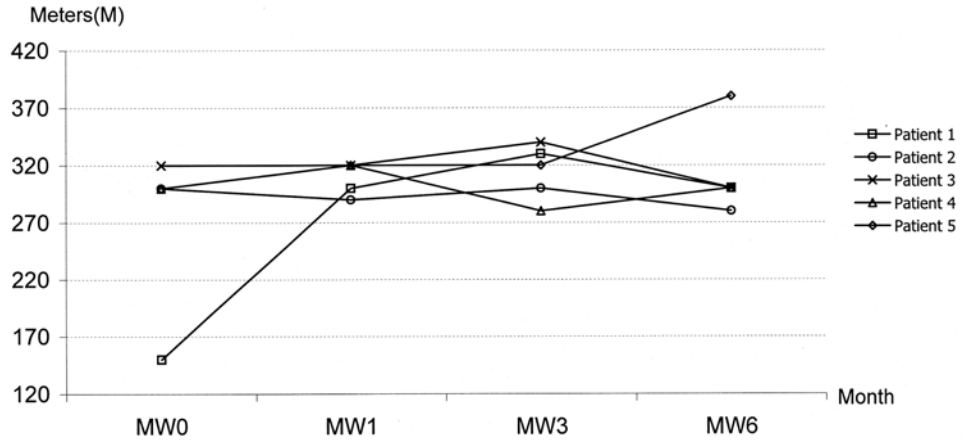

Fig. 2 6-minute walk test in group B patients (post defect closure) at baseline (MW0), 1 month (MW1), 3 months (MW3) and 6 months (MW6), p = 0.320

	Number of patients at baseline	Number of patients after 6 months on Bosentan
NYHA functional class IV	*1*	*0*
NYHA functional class III	*5*	*1*
NYHA functional class II	*5*	*4*
NYHA functional class I	*0*	*6*

Fig. 3 Changing of NYHA functional class among patients
There was no deterioration of functional class

monotherapy for a PAH specific therapy during the 6 months period. No significant side effects were reported during the present study period. The authors collected the data on liver function test at baseline, 1 month and 6 months. There was no significant change in serum aminotransferase (ALT and AST) from baseline during the 6 months of therapy. There was no admission during the follow-up period.

Discussion

The presence of PAH in congenital heart disease has significant impact on both morbidity and mortality[1,2]. With initial congenital left-to-right shunting, the exposure of the pulmonary vasculature to increased blood flow as well as increased pressure may result in pulmonary vascular obstructive disease. As the pulmonary vascular resistance (PVR) approaches or exceeds systemic resistance, the shunt is reversed and cyanosis is evident. Clinical, diagnostic and prognostic data on PAH have been studied predominantly in the adult population with idiopathic pulmonary hypertension (IPAH)[4,5]. Frequently, extrapolation of this data from patients with IPAH was done so that it may be used with the congenital heart disease patients. Currently, chronic therapy of PAH in congenital heart disease patients, are indicated in two groups of patients.

First, the Eisenmenger syndrome is defined as a congenital heart defect that initially causes large left-to right shunt inducing severe pulmonary vascular disease and PAH, with resultant reversal of the direction of shunting and severe oxygen deterioration[1,2,13-15]. Most patients will have impaired exercise tolerance and exertional dyspnea. Although many of them had relatively stable symptoms from preserved right ventricular function, they will eventually suffer from hyperviscosity syndrome and multi-end organ failure. Eisenmenger patients also had earlier clinical deterioration and shorter survival when compared with CHD patients who did not have reverse shunting[1]. Significant morbidities were found in this group of patients, including haemoptysis, pulmonary thromboembolism, stroke or cerebral abscess[1].

Second, patients with CHD who had surgical or transcatheter closure of their lesion, with residual PAH. These patients often are associated with impaired right ventricular function and deserve therapy to lower PVR in order to preserve the right ventricular function.

Presently, the available pulmonary arterial hypertension specific therapies in Thailand are: (i) the derivatives of prostacyclin (PGI_2): beraprost, iloprost. (ii) the phosphodiesterase-5 enzyme inhibitor: sildenafil and (iii) endothelin receptor antagonist: bosentan. In the authors' experience, from an acute pulmonary vasodilator testing study[16], using high dose beraprost (1 mcg/kg/dose) was initially found to be as effective in lowering the PVR as nitric oxide. However, the majority of patients did not tolerate high dose of beraprost, as a study for combination therapies indicated that the average dosage of beraprost was only 60 mcg per day[3]. The effects of combination therapy are shown in a subgroup of patients with some limitation. The use of inhaled iloprost has been shown to exert favorable effects on hemodynamics and exercise capacity. Practically, it can be difficult to dose young children or smaller size adults effectively.

The present study showed significant benefit of bosentan monotherapy for Eisenmenger patients by improving 6MWT from 151 ± 69 meters to 293 ± 61 meters, on the average increased 6MWT of 38 ± 61 meters ($p < 0.001$). The O_2 sat increased from $83 \pm 12.7\%$ to $91.8 \pm 5.6\%$ ($p = 0.038$), on the average increased O_2 sat of $1.4 \pm 0.07\%$. There was no significant change in right ventricular systolic pressure (RVSP). There was also a change in NYHA functional class from Class III and IV to Class I and II in the majority of patients. The therapy was well tolerated by all patients with minimum side effects, in particular change in the elevation of aminotransferase. The benefit of treating patients with Eisenmenger physiology also emphasizes that in this group of patients, if the oxygen saturation can be preserved over some years, the time to end organ failure should be lengthened. Therefore, the improvement in survival time could be achieved. Additionally, the BREATHE-5 study, the first randomized placebo control trial of using bosentan in Eisenmenger patients, showed improvement in exercise capacity and a decrease in pulmonary vascular resistance in patients with Eisenmenger physiology with after only 16 weeks of bosentan therapy[17].

In group B patients, there was also a trend in progress of 6MWT from 274 ± 69 meters to 312 ± 38 meters; however, this was not statistically significant. This may be due to group B patients not being as sick as Eisenmenger patients since their 6MWT and O_2 sat are better than group A patients. However, some of them did have an improvement in the functional class.

Side effects

Despite the previous reports of an increase in hepatic aminotransferase occurred in 10% of the subjects, received large dosage bosentan[8-11]. In both

groups of the presented patients, there was no significant increase in both ALT and AST during the treatment period. All patients received medication throughout the whole 6 months.

Conclusion

In conclusion, the present study shows that long-term use of oral dual endothelin receptor antagonist, bosentan, provides significant clinical (functional class), exercise (6MWT), and oxygen saturation improvements in PAH patients associated with CHD in particular, the group with Eisenmenger physiology. Additional larger detailed studies in the Thai population with long-term dual endothelin receptor antagonist in PAH patients associated CHD are needed to assess the safety and duration of these effects.

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การศึกษาย้อนหลังของการใช้ยาโบเซนแทนในภาวะความดันหลอดเลือดแดงปอดสูงที่เกิดจากโรคหัวใจพิการแต่กำเนิด

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ภูมิหลัง: ภาวะความดันหลอดเลือดแดงปอดสูง (Pulmonary Arterial Hypertension, PAH) มีบทบาทสำคัญต่ออัตราการเป็นโรคและอัตราการตายของผู้ป่วยโรคหัวใจพิการแต่กำเนิด โบเซนแทนเป็นยาที่ต้านการเข้าจับกับตัวรับเฉพาะทั้ง 2 ชนิดของเอนโดทีลีนและได้รับอนุมัติให้ใช้ในผู้ป่วย PAH ที่มี Eisenmenger physiology (EP) ร่วมด้วย การศึกษานี้เป็นการศึกษาย้อนหลังเพื่อศึกษาถึงประสิทธิภาพและความปลอดภัยของยาโบเซนแทนในผู้ป่วยชาวไทยที่มีภาวะ PAH ที่เกิดจากโรคหัวใจพิการแต่กำเนิด

วัสดุและวิธีการ: กลุ่มประชากรของการศึกษาได้แก่กลุ่มผู้ป่วยโรคหัวใจพิการแต่กำเนิดที่ได้รับการรักษาด้วยยาโบเซนแทนเป็นระยะเวลา 6 เดือน ของโรงพยาบาลศิริราช ในช่วงระหว่างเดือนตุลาคม พ.ศ. 2547 ถึงเดือนเมษายน พ.ศ. 2550 เกณฑ์การคัดเข้าคือ: ผู้ป่วยโรคหัวใจพิการแต่กำเนิดที่มี EP ร่วมด้วย หรือผู้ป่วยที่มี PAH รุนแรงหลังจากทำการผ่าตัดหรือใส่สายสวนหัวใจ ลักษณะอาการทางคลินิกประกอบด้วย: ระยะทางที่เดินได้ใน 6 นาที (6MWT) ความอิ่มตัวของออกซิเจน (O_2 sat) การแบ่งระดับความรุนแรงตาม New York Heart Association (NYHA) และ Right Ventricular Systolic Pressure (RVSP) ก่อนได้รับยาโบเซนแทนเทียบกับหลังการได้รับยาโบเซนแทนที่เวลา 1, 3 และ 6 เดือน นอกจากนี้ยังได้รวบรวมอาการและอาการแสดงของเหตุการณ์ไม่พึงประสงค์อีกด้วย

ผลการศึกษา: มีผู้ป่วยทั้งสิ้นจำนวน 11 รายที่มีคุณสมบัติเหมาะกับเกณฑ์การคัดเข้า อายุเฉลี่ย 51.1 $\pm$ 10.1 ปี (13-61 ปี) แบ่งผู้ป่วยออกเป็น 2 กลุ่มคือ; กลุ่ม A (6 ราย) คือ ผู้ป่วย PAH ที่มี EP ร่วมด้วย และกลุ่ม B (5 ราย) คือ ผู้ป่วย PAH หลังทำการผ่าตัด ในผู้ป่วยกลุ่ม A มีระยะทาง 6MWT เพิ่มขึ้นจาก 151 $\pm$ 69 เมตร เป็น 293 $\pm$ 61 เมตร ($p = 0.001$) โดยมีระยะทางเพิ่มขึ้นเฉลี่ย 38 $\pm$ 61 เมตร, O_2 sat เพิ่มขึ้นจาก 83 $\pm$ 12.7% เป็น 91.8 $\pm$ 5.6% ($p = 0.038$) โดยมีความอิ่มตัวเพิ่มขึ้นเฉลี่ย 1.4 $\pm$ 0.07% และไม่พบความแตกต่างอย่างมีนัยสำคัญในค่า RVSP, ในผู้ป่วยกลุ่ม B มีแนวโน้มที่ดีขึ้นของระยะทาง 6MWT จาก 274 $\pm$ 69 เมตร เป็น 312 $\pm$ 38 เมตร แต่ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ พบว่ามีการดีขึ้นของระดับความรุนแรงตาม NYHA ในกลุ่มผู้ป่วยทั้งสองกลุ่ม, ไม่พบการเพิ่มขึ้นของระดับ serum aminotransferase อย่างมีนัยสำคัญในผู้ป่วยแต่ละราย เมื่อสิ้นสุดการรักษาที่ 6 เดือน

สรุป: ยาโบเซนแทนมีประสิทธิภาพในการรักษา PAH ในผู้ป่วยโรคหัวใจพิการแต่กำเนิด โดยเฉพาะอย่างยิ่งในผู้ป่วยที่มี EP ร่วมด้วย ประสิทธิภาพที่เห็นได้ชัดคือมีการดีขึ้นของระยะทาง 6MWT และ O_2 sat