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THE EFFECT OF VASOACTIVE AGENTS IN THE TREATMENT OF PATIENTS WITH PULMONARYARTERIAL HYPERTENSION

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ABSTRACT:

Pulmonary arterial hypertension (PAH) is a rare vascular disease and associated with progressive increases of in pulmonary vascular resistance and pulmonary arterial pressure thatwhich leads to right ventricular failure and death. Idiopathic PAH, connective tissue disease, and congenital heart disease with left to right shunts cause PAH. The diagnosis of PAH is established hemodynamically with a mean pulmonary artery pressure > 25 mmHg at rest and > 30 mmhg mmHg in exercise. PAH must be taken into consideration for in patients which with complaints of progressive dyspnea although they have no underlying pulmonary or heart disease. TransthorasicTransthoracic echocardiography and right heart catheterization are important tools for diagnosis. The treatment as current approaches for treatment are prostanoid analogues, endothelin antagonists, and PDE-inhibitors. In our report we aimed to evaluate the effect of vasoactive agents in the treatment of patients with PAH.

Key words: Pulmonary Arterial Hypertension, Treatment, Sidenafil, Bosentan, Iloprost

PULMONER ARTERİYEL HİPERTANSİYON HASTALARININ TEDAVİSİNDE VAZOAKTİF AJANLARIN ETKİNLİĞİ

ÖZ:

Pulmoner arteriyel hipertansiyon (PAH) nadir gözlenen vasküler bir hastalıktır ve pulmoner vasküler rezistans ve pulmoner arter basıncındaki (PAB) ilerleyici artıs neticesinde sağ kalp yetmezliği ve ölüme neden olmaktadır. Diyopatik PAH, konnektif doku hastalıkları, soldan sağa santlı doğumsal kalp hastalıkları PAH nedenidir. PAH tanısı hemodinamik olarak, ortalama PAB' nın istirahatte 25 mmHg, egzersiz ile 30 mmHg üzerinde olması seklinde tanımlanmaktadır. Ciddi dispnesi olup altta yatan akciğer ve kalp hastalığı bulunmayan kisilerde mutlaka PAH akla getirilmelidir. Transtorasik ekokardiyografi ve sağ kalp kateterizasyonu tanısal olarak büyük önem tasımaktadır. PAH için güncel tedavi yaklasımları prostanoid analogları, endothelin antagonistleri ve PDE-inhibitörlerini içermektedir. Bu çalısmada farklı etiyolojik nedenlere bağlı PAH gelisen hastalarda vazoaktif ajanlarla tedavinin etkinliğinin değerlendirilmesi amaçlandı.

Anahtar kelimeler: Pulmoner Arteriyel Hipertansiyon, Tedavi, Sildenafil, Bosentan, Iloprost

INTRODUCTION

Current treatment approaches in pulmonary arterial hypertension (PAH) are prostanoid analogues, endothelin antagonists, and phosphodiesterase (PDE-) inhibitors.

The long-term effect of these agents in patients with PAH due to different etiologies has not been evaluated in detail. In our report we aimed to describe a case series of 6 patients with

PAH due to different etiologies in whom vasoactive agents improved symptoms, functional class, 6- minute -walking distance, and echocardiographic parameters.

CASE REPORTS

Patient 1

TA- 38-year-old female patient was diagnosed with idiopathic PAH (IPAH) 7 years before on the basis of her clinical status and right heart catheterization (RHC) findings (80 mmHg systolic and 35 mmHg mean pulmonary artery pressure (PAP) without vasoreactivity with calcium channel blockers) and she received sildenafil (3x50 mg/day) for 6 months. RHC was repeated 6 months later and her mean PAP was 10 mmHg lower than the baseline. However, she discontinued sildenafil treatment due to difficulties in obtaining this medication.

She was admitted with worsening dyspnea and edema for 6 months in New York Heart Association (NYHA) functional class III at this time. Her electrocardiogram demonstrated right axis, right ventricular hypertrophy (Figure I). Her transthoracic echocardiogram (TTE) demonstrated pulmonary arterial hypertension (systolic 130 mmHg and mean 65 mmHg

PAP) and right ventricular failure. A spiral computed tomographic (CT) scan and ventilation-perfusion scintigraphy excluded pulmonary thromboembolic and parenchymal disease. She walked 110 meters on a 6- minute -walking test. Antinuclear antibody was positive in low titers. She had thrombocytopenia, leucopenia, and malar erythematous lesions associated with photosensitivity. She was diagnosed with SLE.

Bosentan treatment was initiated at a dose of 62.5 mg twice a day and this was increased to the maintenance dose of 125 mg twice a day. She walked 362 meters in 6 minutes. Her pulmonary systolic pressure decreased to 100 mmHg. She has been on bosentan treatment for 1 year with NYHA class II and has no additional symptoms or laboratory findings and her 6- minute walking test distance has improved to 510 m.

Patient 2

A 48- year-s old female patient was admitted with worsening dyspnea for 2 months in New York Heart Association (NYHA)

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functional class III. Her D-dimer level was 1600 ng/ml at admission. Therefore, she was initially evaluated with computed tomographic and ventilation-perfusion scans and pulmonary parenchymal disease, and pulmonary thromboembolism were excluded. Her immunologic antibodies were negative. TTE showed pulmonary artery hypertension (systolic PAP 105 mmHg) (Figure II-III), enlarged right heart chambers with normal left ventricular function, and normal valvular structure. RHC revealed systolic 110 mmHg and mean 66 mmHg PAP with normal pulmonary capillary wedge pressure (PCWP) and without oxygen step-up and vasodilator response to calcium channel blockers. She was diagnosed with IPAH and bosentan treatment was initiated at a dose of 62.5 mg twice a day and this was increased to the maintenance dose of 125 mg twice a day after one 1 month. After 9 months with bosentan treatment she improved to NYHA Functional class II and 6- minute walking distance increased to 462 meters from 200 meters.

Patient 3

A 37- year-s old female patient had been diagnosed with an inoperable ventricular septal defect (VSD), (pulmonary vascular resistance (PVR) : 1000 dyne/sn/cm-5) PAH, and Eisenmenger syndrome 17 years before. She was admitted with dyspnea, edema, and cyanosis. Her pPhysical examination revealed elevated jugular venous pressure, a loud 2nd heart sound, 1/6 pansystolic murmur in the mesocardiac area, peripheral odema edema, and cyanosis. Right axis deviation and, right ventricular hyphertrophy were noted on electrocardiography. Her cChest- X-ray showed clear lung fields and dilated pulmonary truncus. TTE showed perimembranous VSD (1.4 cm) and, severe PAH (systolic PAP: 130 mmHg). RHC confirmed severe PAH (systolic 148 mmHg and mean 95 mmHg PAP), VSD, normal PCWP (12 mmHg), and elevated PVR (1200 dyne/sn/cm-5) (Figure IV (right atrium), Figure V (right ventricle), Figure VI (pulmonary artery)). Eisenmenger syndrome was established in the transthoracic echocardiographic examination with VSD>1 cm and right to left shunt. She was unresponsive to acute vasodilator testing with calcium channel blockers in RHC. Therefore warfarin and bosentan were started at a dose of 62.5 mg twice a day and increased to the target dose of 125 mg twice a day after 4 weeks. Before treatment she walked 125 meters in the 6-minute walking test. In follow-up visits she had massive epistaxis and therefore warfarin was stopped. Six months after the initiation of bosentan treatment she improved to NYHA functional class II. She walked 386 m at 3 months and 481 m at 9 months in the 6-minute walking test. Her systolic PAP decreased to 110 mmHg on TTE.

Patient 4

A 19-year-old female patient was admitted with progressive dyspnea and cyanosis. Her physical examination showed elevated jugular venous pressure, parasternal lift, a loud P2, 2./6. systolic murmur in left supraclavicular area, and cyanosis in extremities. Right axis, right ventricular hypertrophy was defined on ECG. TTE demonstrated severe PAH (systolic PAP 125 mmHg), dilated right ventricle, right atrium, and pulmonary artery with normal left ventricular function. Pulmonary thromboembolism was excluded in BT angiography. Her immunologic antibodies were negative. In RHC severe PAH (systolic 100 mmHg and mean 78 mmHg PAP), oxygen step-up in the pulmonary artery, and Patent Ductus Arteriosus (PDA) were determined. She was diagnosed with PDA, Eisenmenger syndrome, and PAH. An acute vasodilator test with calcium channel blocker was positive in the hemodynamic evaluation. She walked 210 m in the 6-minute walking test. Warfarin, diltiazem (2x60 mg/day), and bosentan (2x62.5 mg/day and 2x125 mg/day as maintenance dose) were initiated. Her functional capacity improved to NYHA II. After 6 months she walked 368 m in the 6-minute- walking test. However, she discontinued the bosentan treatment due to difficulties in obtaining this medication. She was readmitted with aggravating dyspnea. In her hemodynamic evaluation systolic PAP was 136 (mean PAP 90 mmHg) with normal PCWP and elevated pulmonary vascular resistance. She was unresponsive to acute vasodilator testing and therefore diltiazem was discontinued and bosentan was reinitiated. She walked 540 m in the 6-minute- walking test after 6 months' treatment with bosentan.

Patient 5

A 43-year-old female patient had been diagnosed with PDA, and Eisenmenger syndrome 18 years before. She had had progressive exertional dyspnea for 5 years. TTE showed PDA, right to left shunt, enlarged right heart chambers with systolic PAP 100/40 mmHg, and right heart failure. A spiral computed tomographic scan showed enlarged main (42 mm), left, and right pulmonary arteries. Her pulmonary function test results were normal. The hemodynamic evaluation confirmed PDA, PAH (systolic PAP 147 and mean PAP 91 mmHg), and Eisenmenger syndrome without response to acute vasodilator testing with calcium channel blocker. Inhaled iloprost had been initiated 4 years before with warfarin and, digoxin treatment. She was in NYHA functional class II for 4 years.

In follow-up visits her dyspnea was aggravated. She walked 210 m in the 6-minute- walking test and ceased to walk due to progressive dyspnea. Sildenafil was added to her treatment regimen as 2x50 mg/day. In follow-up visits her symptoms improved to NYHA class II again. After 2 months her 6-minute walking distance increased to 410 m.

Patient 6

A 68-year-old female patient was admitted with chest pain and dyspnea at rest in NYHA functional class IV. She had a history of pulmonary hypertension (PHT) for 10 years and was treated with calcium channel blockers. The physical examination revealed elevated jugular venous pressure, a grade 1-2/6 systolic murmur, parasternal lift, and peripheral edema. Her electrocardiogram showed right ventricular hypertrophy, right axis. She had hypoxemia (PO2 50.4 mmHg, O2 saturation 85%). Her cChest -X-ray demonstrated increased cardiothoracic ratio, and enlarged pulmonary truncus. TTE demonstrated dilated right heart chambers, severe PAH (160 mmHg), and an ostium primum atrial septal defect. The diagnosis of Eisenmenger syndrome was confirmed by right heart catheterization. Inhaled iloprost (10 μg/10 min, 8 inhalations

per day) was initiated. She walked 192 m in the 6 6-minute-walking test at 2 weeks, whereas her functional capacity was New York Heart Association (NYHA) class IV. Therefore 50 mg oral sildenafil was added to the inhaled therapy in increasing doses. At the sixth week with inhaled iloprost and oral sildenafil, her 6-minute walking distance increased to 318 m. During the 4 years of follow up with this combination therapy, there were no serious side effects or clinical deterioration. Her systolic PAP decreased (140 mmHg) and her walking distance improved to 450 m.

DISCUSSION

PAH is consisteds of diseases in which PAP and PVR increase progressively and cause right ventricular failure and death1,2. Endothelial dysfunction, prothrombotic activation, and genetic factors (mutations in the BMPR2 gene) have an important role in the development of PAH3,4. Current treatment approaches in PAH are prostacyclin analogues, endothelin receptor antagonists, type 5 phosphodiesterase inhibitors, and Calcium calcium channel blockers (CCB). CCB should be used according to response to acute vasoreactivity testing in hemodynamic evaluations. Epoprostenol is a first used prostacyclin analogue in PAH with a short half-life, ; therefore continuous IV infusion is required for its efficacy. Epoprostenol infusion improved exercise capacity, and hemodynamic findings in patients with IPAH and scleroderma5. Epoprostenol is not available on the market in our country. Therefore, we prefer iloprost as a prostacyclin analogue. Exercise capacity was increased and hemodynamic findings were improved with inhaled iloprost in patients with IPAH6. Combination therapy with bosentan and iloprost is well tolerated in patients with PAH7,8. Phosphodiesterase (PDE) inhibition causes increased intracellular c-GMP concentrations, which leads to vasodilation in vessel smooth muscle. It has been shown that PDE release and production are increased in patients with chronic PAH9. Sildenafil as a PDE inhibitor was used in some studies and improved hemodynamic findings and exercise capacity10. Endothelin (ET) is a vasoconstrictor and is released from vascular endothelial cells. Bosentan is an oral ET receptor antagonist. Symptoms and exercise capacity of 213 patients with IPAH and connective tissue disease improved in studies with bosentan treatment over 16 weeks. The most common side effects of bosentan is elevation of serum transaminase levels, which is frequent during the first 6 months of treatment, and dilutional anemia11-16. McLaughlin et al. showed that bosentan improved survival rate17. Steiner et al. showed that stable patients with PAH tolerated a switch in treatment from inhaled iloprost to oral bosentan treatment18. Mathai et al. found that combination therapy with bosentan and sildenafil was more efficacious in patients with scleroderma induced PAH19.

Various studies demonstrated the beneficial effects of bosentan in patients with Eisenmenger syndrome20-23. However, Apostolopoulou et al. found that beneficial effects with bosentan appeared in the 16th weeks of the treatment and returned to baseline values in 2 years 24-26. BREATHE-5 was a large randomized, double-blind, placebo-controlled study and bosentan had beneficial effects in patients with Eisenmenger syndrome over 40 weeks in the BREATHE-5 study 27. These agents have some disadvantages; : the high cost and hepatotoxicity of bosentan, poor compliance to iloprost treatment, and the high cost and common side effects of epoprostenol. The prognosis in IPAH is better than in connective tissue disease associated PAH. In recent studies, the relationship between systemic lupus erythematosus (SLE) and PAH was investigated and it was found that the risk of severe PAH was higher than previously thought28,29. Heresi et al. showed that vasoactive treatment with epoprostenol, bosentan, and treprostinil proved clinical and hemodynamic benefits in patients with SLE30. Mok et al. demonstrated in case series that long-term bosentan treatment improved exercise capacity and hemodynamics in patients with SLE-induced-PAH31. Our patient with SLE tolerated bosentan treatment well and her 6-minute walking distance improved prominently without any additional symptoms or findings. In our cases (Table I) one patient with SLE-induced-PAH, one patient with IPAH, and two patients with Eisenmenger syndrome received bosentan treatment. Symptoms, clinical findings, echocardiographic parameters, and 6- minutes walking distance improved in all of the patients. Our 2 patients with Eisenmenger syndrome received combination therapy with iloprost and sildenafil. They tolerated the combination therapy well and have NYHA class II functional status. In our case series all patients (SLE in 1, IPAH in 1, Eisenmenger syndrome in 4) with PAH demonstrated significant improvements in exercise capacity and symptoms. The NYHA functional class improved to class II in all of the patients. Our patients with PAH due to different etiologies had a sustained benefit from long-term vasoactive agent treatment. Therapy with vasoactive agents was safe and well tolerated in our cases.

Table I – Clinical characteristic of the patients

PATIENTS	Age	Etiologies	Syst PAP	Drug	Duration	Walking distance Before	After
Patient I	38	SLE	130 mmHg	Bosentan	1 year	110 m	510 m
Patient II	48	Idiopathic	110 mmHg	Bosentan	9 months	200 m	462 m
Patient III	37	VSD Eisenmenger	130 mmHg	Bosentan	9 months	125 m	481 m
Patient IV	19	PDA Eisenmenger	125 mmHg	Bosentan	6 months	210 m	540 m
Patient V	43	PDA Eisenmenger	147 mmHg	Iloprost Sildenafil	4 years	210 m	410 m
Patient VI	68	Primum ASD Eisenmenger	160 mmHg	Iloprost Sildenafil	4 years	192 m	450 m

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