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PULMONER ARTERİYEL HİPERTANSİYON HASTALARININ TEDAVİSİNDE VAZOAKTİF AJANLARIN ETKİNLİĞİ

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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. İdiyopatik 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.

THE EFFECT OF VASOACTIVE AGENTS IN THE TREATMENT OF PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION
Pulmonary arterial hypertension (PAH) is a rare vascular disease and is associated with progressive increase in pulmonary vascular resistance and pulmonary arterial pressure, which 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 in exercise. PAH must be taken into consideration for patients with complaints of progressive dyspnea even if they have no underlying pulmonary or heart disease. Transthoracic echocardiography and right heart catheterization are important tools for diagnosis. The current treatment approaches 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.

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INTRODUCTION

Current treatment approaches in pulmonary arterial hypertension (PAH) are prostanoid analogues, endothelin antagonists, and phosphodiesterase (PDE-) inhibitors. The long-term effects of these agents in patients with PAH due to different etiologies have not been well evaluated. 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-min walking distance, and echocardiographic parameters.

CASE REPORTS

Patient 1

A 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 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. The 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 m in a 6-min walking test. Antinuclear antibody was positive in low titers. She had thrombocytopenia, leucopenia and malar erythematous lesions associated

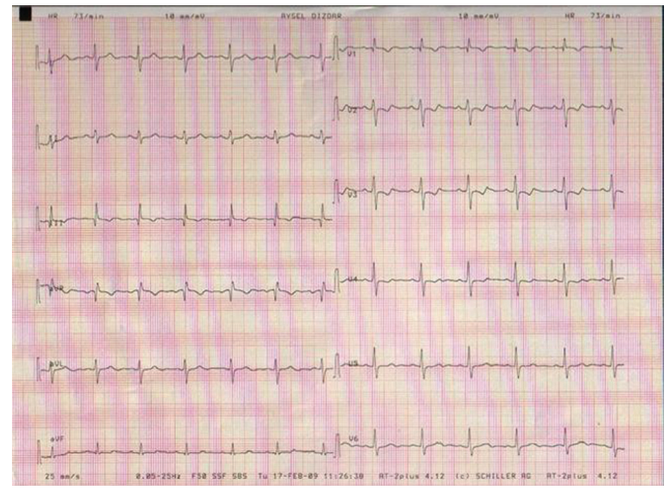

Figure I: ECG demonstrates right ventricular hypertrophy

with photosensitivity. She was diagnosed with SLE. Bosentan treatment was initiated at a dose of 62.5 mg twice a day and increased to the maintenance dose of 125 mg twice a day. She walked 362 m in 6 min. 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-min walking test distance improved to 510 m.

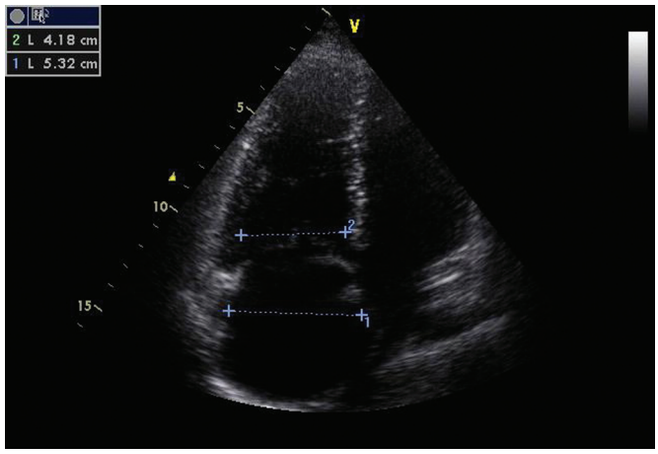

Figure II: Transthoracic echocardiography shows right atrial and ventricular

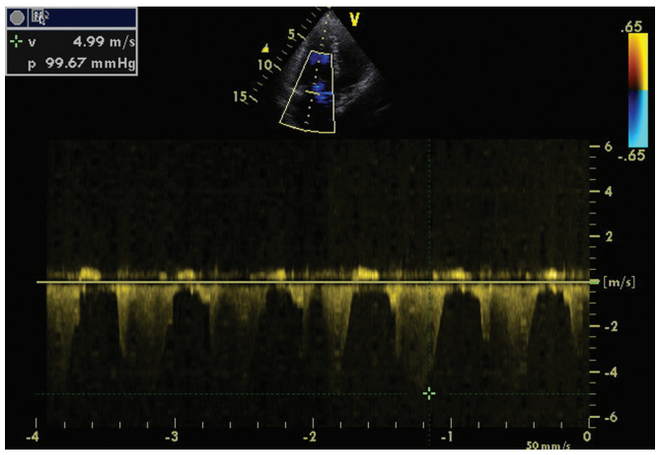

Figure III: Pulmonary artery pressure is 90 mmHg

Patient 2

A 48-year-old female patient was admitted with worsening dyspnea for 2 months in New York Heart Association (NYHA) 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 increased to the maintenance dose of 125 mg twice a day after 1 month. After 9 months with bosentan treatment she improved to NYHA functional class II and her 6-min walking distance increased to 462 m from 200 m.

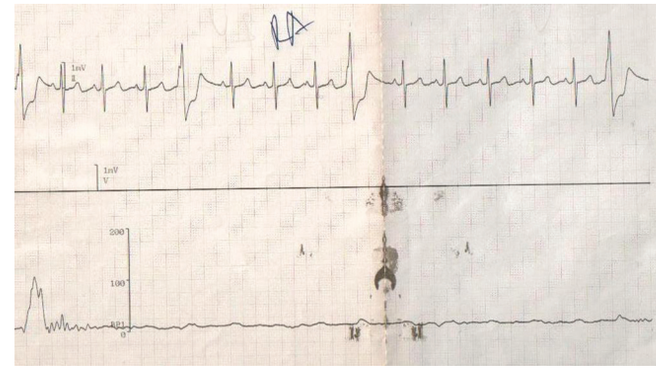

Figure IV:Right atrial pressure during right heart catheterization

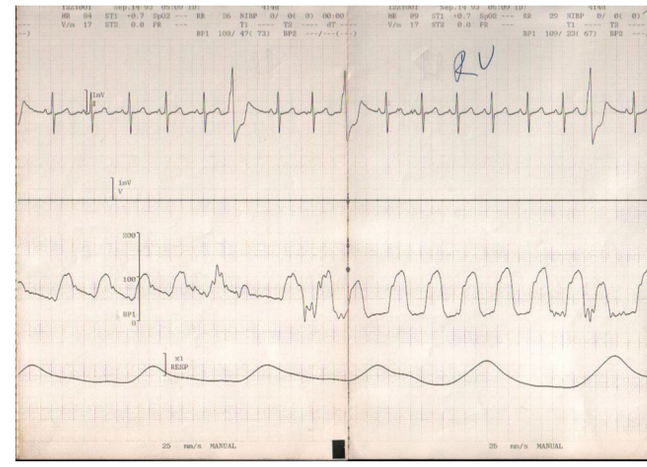

Figure V:Right ventricular pressure during right heart catheterization

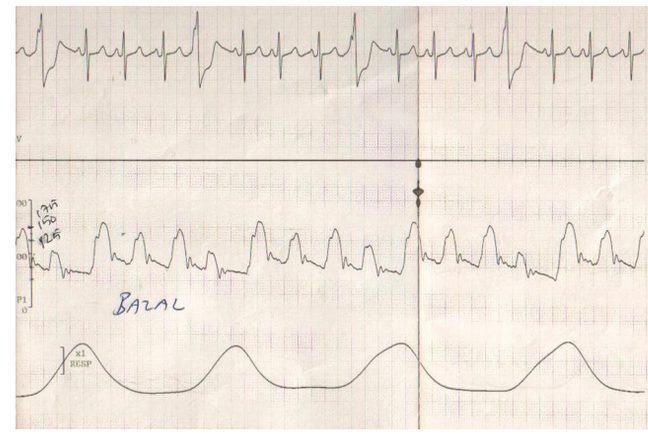

Figure VI:Pulmonary artery pressure during right heart catheterization

Patient 3:

A 37-year-old female patient was diagnosed with inoperable ventricular septal defect (VSD), (pulmonary vascular resistance (PVR): 1000 dyne/s/cm-5) PAH, and Eisenmenger syndrome 17 years before. She was admitted with dyspnea, edema, and cyanosis. Her physical examination revealed elevated jugular venous pressure, a loud 2nd heart sound, 1/6 pansystolic murmur in the mesocardiac area, peripheral edema, and cyanosis. Right axis deviation and right ventricular hypertrophy were noted on electrocardiography. Chest 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/s/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 had walked 125 m in a 6-min 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 on 3rd and 481 m on 9th month in the 6-min 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. Physical examination showed elevated jugular venous pressure, parasternal lift, a loud P2, 2/6 systolic murmur in the left supraclavicular area, and cyanosis in the extremities. Right axis and right ventricular hypertrophy was defined on ECG. TTE demonstrated severe PAH (systolic PAP 125 mmHg), dilated right ventricle, right atrium, 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 pulmonary artery, and patent ductus arteriosus (PDA) were determined. She was diagnosed with PDA, Eisenmenger syndrome, and PAH. Acute vasodilator test with calcium channel blocker was positive in the hemodynamic evaluation. She walked 210 m in a 6-min walking test. Warfarin, diltiazem (2 x 60 mg/day), and bosentan (2 x 62.5 mg/day and 2 x 125 mg/day as maintenance dose) were initiated. Her functional capacity was improved to NYHA II. After 6 months she walked 368 m in a 6-min walking test. However, she discontinued bosentan treatment due to difficulties in obtaining this medication. She was readmitted with aggravating dyspnea. In the 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; therefore diltiazem was discontinued and bosentan was reinitiated. She walked 540 m in a 6-min 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 the NYHA functional class II for 4 years. At follow-up visits her dyspnea was aggravated. She walked 210 m in a 6-min walking test and ceased to walk due to progressive dyspnea. Sildenafil was added to her treatment regimen (2 x 50 mg/day). In follow-up visits her symptoms improved to NYHA class II again. After 2 months her 6-min 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 and right axis deviation. She had hypoxemia (PO_2 50.4 mmHg, O_2 saturation 85%). A chest-X-ray demonstrated an 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 a 6-min walking test at 2 weeks, whereas her functional capacity was NYHA class IV. Therefore, 50 mg oral sildenafil was added to the inhaled therapy in increasing doses. After 6 weeks of inhaled iloprost and oral sildenafil, her 6-min walking distance increased to 318 m. During 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 walking distance improved to 450 m.

DISCUSSION

PAH is a disease in which PAP and PVR increase progressively and cause right ventricular failure and death.[1,2] Endothelial dysfunction, prothrombotic activation, and genetic factors (mutations in the BMPR2 gene) play an important role in the development of PAH.[3,4] Current treatment approaches for PAH are prostacyclin analogues, endothelin receptor antagonists, type 5 phosphodiesterase inhibitors, and calcium channel blockers (CCBs). CCBs should be used according to response to acute vasoreactivity testing in the hemodynamic

evaluation. Epoprostenol is the first prostacyclin analogue used in PAH and has 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 scleroderma.[5] Epoprostenol is not available in this country. Therefore, the prostacyclin analogue we use is iloprost. Exercise capacity was increased and hemodynamic findings were improved with inhaled iloprost in patients with IPAH.[6] Combination therapy with bosentan and iloprost is well tolerated in patients with PAH.[7,8] 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 PAH.[9] Sildenafil as a PDE inhibitor was used in some studies and improved hemodynamic findings and exercise capacity.[10]

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 in 16 weeks. The most common side effect of bosentan is elevation of serum transaminase levels, which is frequent during the first 6 months of treatment and dilutional anemia.[11-16] McLaughlin et al. showed that bosentan improved survival rate.[17] Steiner et al. showed that stable patients with PAH tolerated switch treatment from inhaled iloprost to oral bosentan treatment.[18] Mathai et al. found that combination therapy with bosentan and sildenafil was more efficacious in patients with scleroderma induced PAH.[19] Various studies demonstrated the beneficial effects of bosentan in patients with Eisenmenger syndrome.[20-23] However, Apostolopoulou et al. found that beneficial effects with bosentan appeared in the 16th week of the treatment and returned to baseline values in 2 years.[24-26] BREATHE-5 is a large randomized, double-blind, placebo-controlled study and bosentan had beneficial effects in patients with Eisenmenger syndrome for 40 weeks in the BREATHE-5 study.[27] These agents have some disadvantages, namely the high cost and hepatotoxicity for bosentan, the 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 is higher than previously known.[28,29] Heresi et al. showed that vasoactive treatment with epoprostenol, bosentan, and treprostinil gave clinical and hemodynamic benefits in patients with SLE.[30] Mok et al. demonstrated in a case series that long-term bosentan treatment improved exercise capacity and hemodynamics in patients with SLE-induced PAH.[31] Our patient with SLE tolerated bosentan treatment well and her 6-min walking distance improved substantially 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-min 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.

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 I	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	Hglloprost Sildenafil	4 Years	192 m	450 m

In our case series all patients (SLE in 1, IPAH in 1, and Eisenmenger syndrome in 4) with PAH demonstrated significant improvement 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 received a sustained benefit from long-term vasoactive agent treatment. Therapy with vasoactive agents was safe and well tolerated in our cases.

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