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Research Article

Successful treatment of late-onset pulmonary hypertension after atrial septal defect operation with macitentan: Our center experience

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Abstract

Background: Macitentan significantly improves pulmonary hemodynamics and survival in patients with primary pulmonary hypertension (PPH). Its beneficial effect, however, may be blunted due to the adverse impacts such as anemia and peripheral edema. Pulmonary arterial hypertension (PAH) is a significant consequence of congenital heart disease (CHD). Its presence and severity are associated with increased morbidity and mortality. We tried to evaluate that the effectiveness of the macitentan in patients with late-onset pulmonary hypertension after atrial septal defect operation in our center.

Methods: The effect of a single dose of macitentan (10 mg) on pulmonary hemodynamics, functional capacity was examined in four patients with late-onset pulmonary hypertension after atrial septal defect operation.

Results: The macitentan significantly improved mean pulmonary artery pressure (MPAP), cardiac output (CO), tricuspid annular plane systolic excursion (TAPSE), right ventricle systolic wave(RVS'), 6-minute walking test and NT-proBNP levels compared with before treatment.

Conclusions: Macitentan can be used in patients with late-onset pulmonary hypertension after shunt operation especially atrial septal defect.

Introduction

Pulmonary arterial hypertension (PAH) associated with congenital heart disease is usually the result of a sizeable systemic-to-pulmonary shunt. It often leads to right ventricular failure and early death [1]. The prevalence of this phenomenon differs in various reports. The Euro Heart Survey on adult congenital heart disease (CHD), which is a retrospective cohort study with a five-year follow-up, reported PAH in 28% of patients [2], while a Dutch registry showed a PAH prevalence of only 4.2% [3]. The guidelines ensure recommendations for the management of PAH-CHD [4,5]. However, evidence to support the use of PAH-specific therapies in CHD is limited, and the administration is not standardized, with variation between treating centers and clinicians. The dual endothelin-receptor antagonist macitentan was developed by modifying the structure of bosentan to increase efficacy and safety [5]. Macitentan is characterized by sustained receptor binding and enhanced tissue penetration [6,7]. It can be used as pulmonary arterial hypertension [8]. Two dose levels (3 and 10 mg) were studied; macitentan reduced the risk of a morbidity/mortality event vs. placebo (10 mg dose, risk reduction 45 %, p>0.001; 3mg dose, risk reduction 30%, p=0.01) [9]. This study aimed to evaluate the macitentan therapy of adults with corrected congenital heart diseases(especially atrial septal defect) and pulmonary arterial hypertension in a single center in our center.

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Methods

Four patients with late-onset pulmonary hypertension after shunt operation were evaluated after 3 months of macitentan therapy. Macitentan had been given as a result of nonresponsiveness to vasoreactivity test. Each patient gave written informed consent to participate in the study which was approved by the local ethical committee Firat. The diagnosis pulmonary arterial hypertension was based on a raised MPAP of ≥25mm Hg and the diagnostic criteria published by [4]. There were atrial septal defect operation stories all of the patients. All of the patients were diagnosed with pulmonary arterial hypertension by pulmonary hypertension council (included cardiologist, and pulmonologist). The disease is defined as late-onset pulmonary hypertension after atrial septal defect operation (acquired pulmonary arterial hypertension) (Table 1). All patients were treated with macitentan 10 mg. They were reevaluated after three months.

Statistical analyses

Data were analyzed descriptively using the IBM SPSS 23.0. Baseline variables were recorded and are presented as mean. Intraindividual comparison of the hemodynamic variables measured at baseline and after macitentan was made using the two-sided Wilcoxon U test for paired data. P values below 0.05 were considered statistically significant.

Results

The effect of macitentan on pulmonary hemodynamics was tested in four patients (female) with a proven diagnosis of pulmonary arterial hypertension(acquired pulmonary arterial hypertension after atrial septal defect operation) for a mean period of 6 months. Patients participated in a hemodynamic study that included right heart catheterization at baseline and month 6. Patients had significant decreases in pulmonary vascular resistance, and significant increases in the cardiac output, as compared with the basal term. The 6-minute walk distance had increased in all patients ($p<0.05$) (Table 1).

Discussion

Macitentan considerably diminished morbidity and mortality among patients with pulmonary arterial hypertension. Because pulmonary arterial hypertension is a chronic, life-threatening disease, data from long-term outcome studies are required to assess the impact of therapy on disease progression. Updated guidelines for clinical research on pulmonary arterial hypertension support the use of these long-term outcome studies [10]. Our trial showed that macitentan therapy significantly improved

Table 1: Haemodynamic values in patients with acquired pulmonary arterial hypertension at baseline and after treatment with macitentan.

	1.Patient	2.Patient	3.Patient	4.Patient	P value
Age	41	71	68	36	
Gender	Female	Female	Female	Female	
Shunt Operation	ASD	ASD	ASD	ASD	
Operation Time(year)	12	19	11	7	
MPAP(mmHg)	28-15	30-20	25-15	30-20	<0.05
CO(L/min)	2.7-3.5	2.2-3.6	2.3-3	2.6-3.5	<0.05
PVR(Wood)	5-2	4-1	4-1	7-2	<0.05
Nt-ProBNP(pg/dl)	450-205	550-201	480-180	425-115	<0.05
TAPSE	11-17	13-16	13-17	11-18	<0.05
RVS'(cm/s)	6-9	7-11	7-13	8-12	<0.05
sPAB(mmHg)	50-30	55-27	52-25	60-30	<0.05
6-MWT(meters)	225-450	300-485	285-425	300-510	<0.05

MPAP=Mean pulmonary artery pressure; MSAP=Mean systemic arterial pressure; PCWP=Pulmonary capillary wedge pressure; CI=Cardiac index; CO=Cardiac output; PVR=Pulmonary vascular resistance; 6-MWT=6 Minute Walking Test; TAPSE=Tricuspid Annular Plane Systolic Excursion; RVS'=Right Ventricle Systolic Wave; sPAB=Systolic pulmonary artery pressure.

pulmonary hemodynamics in four patients with late-onset pulmonary hypertension after shunt operation within six months. More importantly, the macitentan theraphy enhanced parameters closely linked to long-term effects of treatment and survival in pulmonary arterial hypertension such as MPAP and CO [11]. These results suggest that macitentan at 10mg dose allows for stable treatment of this patient group.This is the first trial in these patient group.

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