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218 Inhaled treprostinil is a potent pulmonary vasodilator in severe pulmonary hypertension

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Background: Treprostinil has been approved for therapy of PAH (US and Canada) as continuous subcutaneous infusion. However, local pain at the infusion site is a major drawback. Inhaled therapy with another stable prostacyclin analogue (iloprost) has been approved for PPH (EMEA). In this study we investigated the acute hemodynamic response to inhaled treprostinil.
Methods: Open-label, single blind placebo-controlled clinical study. After placement of a Swan-Ganz catheter and a femoral artery line, patients inhaled solvent solution (placebo) (n=8) or treprostinil for 6 min (OptiNeb ultrasound nebulizer, Nebu-tec, Germany) in concentrations of 16, 32, 48, and 64 μg/ml (n=6, 6, 6, and 3 patients). Measurement was performed before and after 0, 15, 30, 60, 90, 120, 150 and 180 min. The mean area between the placebo and the treprostinil curves (ABC186) was calculated (baseline=100%).
Results: We investigated idiopathic PAH (n=10), collagen vascular disease (n=5), chronic thromboembolic disease (n=9), and pulmonary fibrosis (n=5), f/m = 19/10, age 56 ± 3 years, PAP, PAWP, and CVP 51.3 ± 2.2, 9.2 ± 0.8, and 6.6 ± 0.6 mmHg, CO 4.4 ± 0.3 l/min, SvO2 62.3 ± 1.2%, PVR 885 ± 72 dyn s cm^{-5}. At 16μg/ml there were no significant adverse events. Headache, cough or bronchoconstriction were observed in 2, 1, and 2 patients at 32, 48, and 64 μg/ml. These were mild and transient in all patients but one (64 μg/ml) who complained of major headache for 1 hour. Placebo inhalation was followed by slowly increasing PVR. Compared to this, the maximum treprostinil effect was reached after about 50 min and half-maximal effects at about 110 min. The ABC186 for PVR was –24.7 ± 4.4, -28.7 ± 4.9, and –29.0 ± 4.7%; PAP –14.4 ± 3.3, -13.5 ± 5.2, -13.1 ± 2.6%; SAP –5.1 ± 3.0, -6.0 ± 3.1, -3.8 ± 2.1% at 16, 32 and 48 μg/ml.
Conclusion: Treprostinil inhalation results in a significant long-lasting pulmonary vasodilatation. With the applied technology, at a concentration of 16μg/ml, near maximal pulmonary vasodilatation is achieved without adverse effects. At higher doses, local and systemic side effects may occur, whereas pulmonary selectivity is preserved.
This study was supported by Lung Rx.

219 The endothelin-receptor antagonist bosentan for the treatment of pulmonary arterial hypertension associated with congenital heart defects

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Background: Treatment with the oral dual endothelin-receptor antagonist bosentan has been shown to be an effective alternative option to intravenous epoprostenol in functional class (FC) III idiopathic pulmonary arterial hypertension (PAH) patients. In patients with PAH associated with congenital heart defects (CHD), an improvement of exercise capacity and hemodynamics has been demonstrated with epoprostenol in one uncontrolled study (Rosenzweig et al. Circulation 1999; 99: 1858-65).
The aim of this retrospective study was to evaluate the efficacy and safety of bosentan in FC III-IV CHD-PAH patients.
Study population consisted in 24 patients (22 females, mean age 35 ± 15 years [8-68]) with CHD-PAH: atrial septal defect (ASD: 13), ventricular septal defect (VSD: 4), partial abnormal pulmonary venous return (3, associated with ASD in 2 and repaired common atrium in 1), patent ductus arteriosus (PDA: 2), VSD associated with PDA (1), aortopulmonary window (1). Four patients had undergone previous cardiac surgery.
Patients had deteriorated despite conventional therapy (including oral anticoagulants, oxygen, diuretics) and were treated with chronic oral bosentan.
Results: Before starting bosentan, 22 patients were in FC III and 2 in FC IV, with a resting O2 saturation (SaO2) of 89 ± 9%. Mean 6-min walk distance (6MWD) was 288 ± 94 m and mean Borg index 3.0 ± 1.9. At last evaluation performed after 10 ± 9 months of bosentan treatment, 1 patient was in FC I, 8 were is FC II, 13 remained in FC III and 2 in FC IV. The mean 6MWD improved by 49 m (349 ± 85 m, p = 0.008) with no change in Borg index (3.0 ± 1.8) and resting SaO2 (89 ± 6%). There were no differences between pre and post-tricuspid shunt subgroups in terms of baseline characteristics and response to bosentan therapy. After 13 ± 9 months of follow-up, all patients are alive on bosentan, but 3 (1 ASD, 1 VSD, 1 aortopulmonary window) required combination therapy with intravenous epoprostenol after 5, 7 and 9 months on bosentan.
Conclusion: Chronic oral bosentan treatment improves exercise capacity in patients with PAH associated with CHD who deteriorated despite conventional therapy. Bosentan had no adverse effect on arterial oxygen saturation. As previously demonstrated in patients with idiopathic PAH, long term bosentan may be an important therapeutic option for patients with PAH associated with CHD.

220 Sildenafil in the treatment of primary pulmonary hypertension

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Backgroud: The role of sildenafil as a pulmonary vasodilator is being extensively evaluated in the treatment of pulmonary hypertension.
Aim: This was a prospective study to assess the benefit of adding sildenafil in patients with high pulmonary artery pressures secondary to atrial septal defect (ASD), already receiving the conventional therapy.
Methods: Thirty consecutive patients with moderate to severe primary pulmonary hypertension were included in this study. All the patients were diagnosed previously and were receiving the conventional therapy with digoxin, diuretic and a calcium channel blocker. Sildenafil was added in the dose of 50 mg twice a day without changing the previous regimens. Changes in the New York Heart Association (NYHA) symptom class, distance covered during the six minute walk test and modified Borg dyspnea score were evaluated monthly. Acceptance of the new drug was assessed every week in the first month and then at the monthly follow up. Echocardiography and Doppler study was undertaken at baseline and every month for a period of six months. The parameters studied were the pulmonary artery systolic pressure (PASP) by tricuspid regurgitation (TR) jet and pulmonary artery diastolic pressure (PADP) by pulmonary regurgitation (PR) jet.
Results: Mean age of the subjects was 42.6±9.3 years. Twenty seven (90%) were females and 3 (10%) were males. Sildenafil was well tolerated and there was no dropout because of undesireable effects of the drug. Changes in the heart rate and systemic blood pressure were not significant enough to warrant withdrawl of the drug. Two patients died during the follow-up period. At the beginning of the therapy, 22 (73.3%) patients were in NYHA Class III or IV while at the end of six months, only 8 patients remained in either of these classes ($p<0.05$). By the 6 min walk test, functional capacity improved from 181.5±122.4 meters to 302.7±150.3 meters $p(<0.05)$. Modified Borg dyspnea score improved from 5.6±1.2 to 3.3±1.1 ($p<0.05$). PASP by TR jet (mmHg) was down from 81.3±14.7 to 51.4±11.7 ($p<0.05$). PADP by PR jet (mmHg) reduced from 56.2±11.7 to 33.4±9.1 ($p<0.05$).
Conclusion: Sildenafil is well tolerated, improves symptoms, and reduces the systolic and diastolic pulmonary artery pressures in patients with moderate to severe primary pulmonary arterial hypertension.

REVISITING THE ELECTROCARDIOGRAM AND ELECTROPHYSIOLOGIC MARKERS OF ARRHYTHMIC EVENTS

221 Prevalence of brugada-type ecg in an apparently healthy european population

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Background: The Brugada Syndrome ECG is characterized by ST-segment elevation in right precordial leads and elevated risk of lethal arrhythmias in absence of identifiable structural heart disease. Few data are available on the Brugada type ECG, especially in Europeans. No epidemiological study has applied the diagnostic criteria recently proposed by the Study Group of the Molecular Basis of Arrhythmias of the ESC.
Methods: We analysed the ECG and clinical data of apparently healthy European adults undergoing routine medical examinations for occupational reasons. At each examination subjects underwent a medical interview, physical examination, blood pressure measurement and 12-lead ECG. Enrolment was confined to persons without a history of heart disease at the time of first attendance in whom at least one 12-lead ECG of good quality was recorded. The ECG records of all 7483 subjects (89.6% male, age 29,5±10,8 years at first attendance) were reviewed by three cardiologists. We reviewed 1,97±2,1 ECGs for each subject. We considered a patient having a Brugada ECG pattern if 2 or more of the cardiologists judged that at least one of that persons ECGs fulfilled the criteria of the ESC Study Group.
Results: The Brugada pattern was present in 26 patients (0.35%), all male (table). In 17 cases (65.4%), information was available about the progress of the subject subsequent to the ECG on which the Brugada pattern was first recorded. No sudden death or cardiac arrhythmia was recorded among these patients in a follow-up of 5.2±4.6 years (total follow-up 87.8 patient-years).

	Total	Pattern 1	Pattern 2	Pattern 3	Tot. Brugada
Pts (n)	7383	2	21	3	26
Male	6618	2	21	3	26
Female	765	0	0	0	0
Male prevalence (*10000)	–	3,02	31,73	4,53	39,29
Total Prevalence (*10000)	–	2,71	28,44	4,06	35,22