Dehydroepiandrosterone (DHEA) improves pulmonary hypertension in chronic obstructive pulmonary disease (COPD): A pilot study

La déhydroépiandrostérone (DHEA) améliore l’hypertension pulmonaire associée à la bronchopneumopathie chronique obstructive : étude pilote

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Abstract

Objectives. – It was previously shown that dehydroepiandrosterone (DHEA) reverses chronic hypoxia-induced pulmonary hypertension (PH) in rats, but whether DHEA can improve the clinical and hemodynamic status of patients with PH associated to chronic obstructive pulmonary disease (PH-COPD) has not been studied whereas it is a very severe poorly treated disease. Patients and methods. – Eight patients with PH-COPD were treated with DHEA (200 mg daily orally) for 3 months. The primary end-point was the change in the 6-minute walk test (6-MWT) distance. Secondary end-points included pulmonary hemodynamics, lung function tests and tolerance of treatment. Results. – The 6-MWT increased in all cases, from 333 m (median [IQR]) (257; 378) to 390 m (362; 440) (P < 0.05). Mean pulmonary artery pressure decreased from 26 mmHg (25; 27) to 21.5 mmHg (20; 25) (P < 0.05) and pulmonary vascular resistance from 4.2 UI (3.5; 4.4) to 2.6 UI (2.5; 3.8) (P < 0.05). The carbon monoxide diffusing capacity of the lung (DLCO % predicted) increased significantly from 27.4% (20.1; 29.3) to 36.4% (14.6; 39.6) (P < 0.05). DHEA treatment did not change respiratory parameters of gas exchange and the 200 mg per day of DHEA used was perfectly tolerated with no side effect reported. Conclusion. – DHEA treatment significantly improves 6-MWT distance, pulmonary hemodynamics and DLCO of patients with PH-COPD, without worsening gas exchange, as do other pharmacological treatments of PH (trial registration NCT00581087).

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Résumé

Objectifs. – Nous avons montré précédemment que la déhydroépiandrostérone (DHEA) améliore l’hypertension pulmonaire induite par l’hypoxie chronique chez le rat, mais l’effet clinique et hémodynamique de la DHEA chez des patients atteints d’hypertension pulmonaire associée à la bronchopneumopathie chronique obstructive (BPCO) n’a pas été étudié. Patients et méthodes. – Huit patients avec hypertension pulmonaire associée à la BPCO ont reçu de la DHEA (200 mg par jour par voie orale) pendant trois mois. Le critère principal d’évaluation était la modification du test de marche de six minutes (6-MWT). Les critères secondaires incluaient l’hémodynamique pulmonaire, les tests de fonction pulmonaire et la tolérance au traitement. Résultats. – Le 6-MWT a augmenté dans tous les cas, de 333 m (médiane, quartiles) (257; 378) à 390 m (362; 440) (p < 0.05). La pression artérielle pulmonaire moyenne est passée de 26 mmHg (25; 27) à 21,5 mmHg (20; 25) (p < 0.05) et la résistance vasculaire pulmonaire de 4,2 UI (3,5; 4,4) à 2,6 UI (2,5; 3,8) (p < 0.05). La capacité de diffusion pulmonaire du monoxyde de carbone (DLCO %) a augmenté significativement de 27,4 % (20,1; 29,3) à 36,4 % (14,6; 39,6) (p < 0.05). Le traitement par la DHEA n’a pas changé les paramètres respiratoires des échanges gazeux et la tolérance a été bonne sans aucun effet secondaire. Conclusion. – Dans cette étude, le traitement par la DHEA de patients

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atteints d’hypertension pulmonaire associée à la BPCO améliore significativement le test de marche de six minutes et l’hémodynamique pulmonaire sans aggraver les échanges gazeux (NCT00581087).

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1. Introduction

Chronic obstructive pulmonary disease (COPD) results from an inflammatory process affecting the Airways and lung parenchyma. COPD alters gas exchange leading to hypoxemia that triggers hypoxic pulmonary vasoconstriction [1]. Maintained pulmonary vasoconstriction is accompanied by vascular remodeling, that importantly causes thickening of the arterial wall and increases blood resistance by reducing the vessel diameter [2]. Pulmonary hypertension (PH), defined as an increase of the pulmonary artery pressure, is a severe complication in the natural history of COPD and has been reported in 20 to 91% of patients with severe COPD and/or emphysema [2,3]. Patients with COPD and PH have shorter survival than patients with normal pulmonary artery pressure [4], and survival is inversely related to pulmonary vascular resistance [3]. Moreover, the presence of PH is one of the best predictors of mortality [5]. To date, the treatment of PH secondary to COPD (PH-COPD) has been disappointing [2]. On the one hand, vasodilators used in primitive forms of PH, reduce the pulmonary artery pressure, but they may also worsen arterial oxygenation [6–9]. On the other hand, oxygen therapy, while increasing arterial oxygen pressure (PaO2) can slow or reverse PH progression, but requires a long term inhaled administration [10,11].

Dehydroepiandrosterone (DHEA) is a steroid derived from cholesterol, and mostly secreted as its sulfate by adrenals in the human beings [12,13]. It is the most abundant circulating steroid, DHEA-S serving of reservoir for DHEA that is released by sulfatase produced in a wide range of tissues. The age-related decline in blood DHEA and DHEA-S [14–16] may be causally related to the development of some pathological events associated with aging; this has been suggested for a possible pathophysiological role of DHEA-S in cardiovascular diseases [17]. In a rat model of chronic hypobaric hypoxia, we have previously demonstrated that DHEA prevents and decreases hypoxic pulmonary hypertension and associated right ventricle hypertrophy [18]. Very little DHEA is secreted by endocrine glands in rats, and the active doses of DHEA used in our experiments, for chronic oral as well as intravascular acute administrations, were of pharmacological level and significance. We therefore hypothesized that an appropriate amount of DHEA may benefit to patients with PH-COPD and conducted a proof of concept pilot study over a 12-week period of DHEA administration.

2. Methods

2.1. Subjects

Eight patients with pulmonary hypertension (New York Heart Association functional class III or IV) (Table 1) associated with COPD were included in this study. Inclusion criteria were: COPD was defined by FEV1/FVC less than 70% of reference values; resting mean pulmonary artery pressure (assessment by right pulmonary catheterization) greater or equal to 25 mmHg with mean pulmonary capillary wedge pressure less or equal to 15 mmHg, PaO2 less or equal to 60 mmHg at rest or PaO2 greater or equal to 60 mmHg associated with significant fall in O2 saturation with exercise. In two patients, there was 6-month permanent oxygen treatment permitting to interpret the possible effect of DHEA treatment. Exclusion criteria were: clinical or respiratory instability during the 3 months before the inclusion in the study; corticosteroid therapy (>0.5 mg/kg per day of prednisolone or as equivalent); hepatic (prothrombin time less than 50%) or renal (creatininemia greater than 130 μmol/L) failure; diabetes; left ventricular dysfunction; PSA (prostatic antigen greater than 2.5 ng/mL) and past history or diagnosis of cancer. The study was conducted according to Good Clinical Practices. The study protocol was approved by the Regional Ethics Review Board. Written informed consent was obtained for all patients and investigations were conducted according to the institutional guidelines and to the Helsinki principles. This study was registered in clinicaltrials.gov (NCT00581087).

2.2. Study design

The dose of oral DHEA administered was 200 mg once daily for 3 months. At baseline and after 3 months of treatment, evaluation included a 6-minute walk test (6-MWT), Borg dyspnea index, measurement of systolic and diastolic blood pressure, right heart catheterization, lung function testing and serum DHEA levels were performed.

The primary end-point was the change from baseline in exercise capacity as determined by the 6-MWT after 3 months of treatment. Secondary end-points included pulmonary artery hemodynamic parameters, respiratory variables and tolerance of treatment. Possible adverse events and side effects were recorded throughout the study (blood pressure, acne, hirsutism).

DHEA was purchased from Cooper (France) and tablets were prepared by the pharmaceutical unit of Bordeaux University Hospital (France) with the authorization of the French “FDA” Agency (Afssaps).

2.3. Procedures

2.3.1. 6-minute walk test

The 6-minute walk test was performed in all patients using a standardized protocol in accordance with the American Thoracic Society Statement 2002 [19].

2.3.2. Right heart catheterization

Right heart catheterization was performed in all patients, but in two patient’s measurements was not obtained because of technical difficulties. A flow-directed balloon-tipped 7F Swan-Ganz catheter (131HF7; Baxter Healthcare Corp., Irvine, USA)
Table 1
Baseline characteristics of the patients.

<table>
<thead>
<tr>
<th></th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>NYHA class</th>
<th>Tobacco</th>
<th>Diagnosis</th>
<th>Concomitant treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>54</td>
<td>F</td>
<td>IV</td>
<td>Yes</td>
<td>COPD</td>
<td>Bronchodilators</td>
</tr>
<tr>
<td>(2)</td>
<td>52</td>
<td>M</td>
<td>IV</td>
<td>No</td>
<td>COPD</td>
<td>Bronchodilators</td>
</tr>
<tr>
<td>(3)</td>
<td>56</td>
<td>F</td>
<td>IV</td>
<td>No</td>
<td>COPD</td>
<td>Nocturnal oxygen</td>
</tr>
<tr>
<td>(4)</td>
<td>41</td>
<td>F</td>
<td>II</td>
<td>Yes</td>
<td>COPD</td>
<td>Bronchodilators</td>
</tr>
<tr>
<td>(5)</td>
<td>65</td>
<td>M</td>
<td>III</td>
<td>Yes</td>
<td>COPD</td>
<td>Bronchodilators, diuretics, nocturnal oxygen</td>
</tr>
<tr>
<td>(6)</td>
<td>72</td>
<td>M</td>
<td>II</td>
<td>Yes</td>
<td>COPD</td>
<td>Bronchodilators</td>
</tr>
<tr>
<td>(7)</td>
<td>64</td>
<td>M</td>
<td>IV</td>
<td>No</td>
<td>COPD</td>
<td>Bronchodilators, Ca channel blocker</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease; Ca: calcium; NYHA: New York Heart Association; yrs: years.

Table 2
Clinical and pharmacological variables.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>3 months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-minute walk test distance (m)</td>
<td>333 (257; 378)</td>
<td>390 (362; 440)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Dyspnea score (Borg index)</td>
<td>5.5 (4; 6.8)</td>
<td>4.7 (4; 8)</td>
<td>ns</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>125 (120; 145)</td>
<td>140 (140; 140)</td>
<td>ns</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mmHg)</td>
<td>80 (75; 80)</td>
<td>80 (77; 80)</td>
<td>ns</td>
</tr>
<tr>
<td>Serum DHEA (nmol/L)</td>
<td>11.2 (9.6; 12.3)</td>
<td>23.4 (19.7; 38.4)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Data are presented as medians and quartiles (Q1; Q3); ns: non-significant; DHEA: dehydroepiandrosterone.

was inserted via the internal jugular vein. Cardiac output was determined by the direct Fick method.

2.3.3. Lung function testing

Pulmonary mechanics were evaluated by body plethysmography. Blood gases and carbon monoxide diffusion capacity were also measured. All testing was performed according to the European Respiratory/American Thoracic Society guidelines [20].

2.4. Statistical analysis

Data are presented as medians and quartiles (first and third quartiles) in box and whisker diagrams. A P-value <0.05 was considered to be significant. A Wilcoxon paired rank test was used to compare data obtained before and after DHEA administration.

3. Results

We investigated the efficacy and safety of DHEA in eight patients (five men, three women, 41 to 72 years old) with PH-COPD in the absence of specific pulmonary vasodilator treatment. Patient characteristics are given in Table 1. For the two patients treated with oxygen (patients 3 and 5), there was no modification in oxygen therapy during the study period.

After 3 months of daily intake of DHEA, the 6-MWT distance increased by 57 m (17%), from 333 m (257; 378) to 390 m (362; 440) (P < 0.05) (Fig. 1 and Table 2).

Results of the hemodynamic measurements are presented in Table 3. Mean pulmonary artery pressure significantly decreased from 26 mmHg (25; 27) to 21.5 mmHg (20; 25) (P < 0.05) (Fig. 2). Systolic pulmonary artery pressure also decreased significantly from 40 mmHg (37; 42) to 30 mmHg (29; 32) (P < 0.05) and diastolic pulmonary artery pressure from 18 mmHg (18; 18.7) to 14 mmHg (12; 16) (P < 0.05). Pulmonary vascular resistance decreased significantly from 4.2 UI (3.5; 4.4) to 2.6 UI (2.5; 3.8) (P < 0.05). Pulmonary capillary wedge pressure and cardiac output remained unchanged.

The pulmonary function characteristics of the patients before and after treatment with DHEA are reported in Table 4. Forced expiratory volume in one second (FEV1), vital capacity (VC), arterial partial oxygen pressure (PaO₂), arterial partial carbon monoxide (PaCO₂) and arterial pH were unchanged.

Table 3
Pulmonary hemodynamic variables.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>3 months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>80 (76; 81)</td>
<td>73 (68; 76)</td>
<td>ns</td>
</tr>
<tr>
<td>Systolic pulmonary arterial pressure (mmHg)</td>
<td>40 (37; 42)</td>
<td>30 (29; 32)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic pulmonary arterial pressure (mmHg)</td>
<td>18 (18; 18.7)</td>
<td>14 (12; 16)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mmHg)</td>
<td>26 (25; 27)</td>
<td>21 (20; 22)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (IU)</td>
<td>4.2 (3.5; 4.4)</td>
<td>2.6 (2.5; 3.8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mmHg)</td>
<td>9.5 (5.7; 10.5)</td>
<td>8.1 (6.7; 8.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Cardiac output (l/mn)</td>
<td>5.7 (4.3; 6.1)</td>
<td>5.5 (4.3; 6)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Data are presented as medians and quartiles (Q1; Q3); ns: non-significant.
dioxide (PaCO₂), hemoglobin oxygen saturation (SaO₂) and mixed venous oxygen saturation (SvO₂) remained unchanged (Table 4). In contrast, the carbon monoxide diffusing capacity of the lung (DLCO % predicted) increased significantly from 27.4% (20.1; 29.3) to 36.4% (14.6; 39.6) (P < 0.05).

Mean serum free DHEA concentration (performed in the morning before taking the DHEA) increased significantly from 11.2 nmol/L (9.6; 12.3) to 23.4 nmol/L (19.7; 38.4) (P < 0.05). Systolic and diastolic general blood pressure remained stable over the treatment period (Table 2). No side effect was reported during the study (acne, hirsutism).

4. Discussion

This pilot study shows that oral DHEA treatment in PH-COPD patients significantly improves clinical indices of disease severity including 6-MWT distance and pulmonary hemodynamics. Moreover, DHEA treatment increases DLCO without adverse effect on gas exchange.

The 6-MWT is frequently used to estimate the efficacy of therapies in various cardiopulmonary diseases as well as a prognostic marker in PH [21]. In COPD, the distance achieved during the 6-MWT correlates well with other measures of quality of life [22]. The achieved gain in distance in the 6-MWT in our patients (57 m) is similar to that achieved with widely prescribed treatments of PH such as Bosentan or Epoprostenol [23]. In the present study, the improvement in the 6-MWT remarkably observed in all the eight patients, is substantiated by the hemodynamic improvement, showing a significant decrease in both pulmonary artery pressure and pulmonary vascular resistance. For one patient, there was no change in pulmonary hemodynamics, but it can be considered as a good result because of the usual rapid trend towards worsening of PH in untreated patients [4]. Two patients received oxygen that, according to previous studies, does not improve the pulmonary artery pressure [24,25].

As indicated before, the original decision to use DHEA in human beings was taken from studies in rats, even considering that physiologically in rodents there is insignificant blood concentration of DHEA as compared to human beings [12]. We had noted the relatively high dose of DHEA necessary for efficiency in the rat hypoxic model. In this study, the choice of a pharmacological dose of 200 mg/d was acceptable by the already well tolerated studies in systemic lupus erythematosus [26].

The beneficial use of DHEA in pulmonary hypertension has been observed in several animal models. We first demonstrated that DHEA can prevent and reverse chronic hypoxic pulmonary
hypertension in a hypoxic rat model [18]. This finding was also observed in the monocrotaline-induced pulmonary hypertension rat model [27]. Some clues regarding the cellular mechanisms involved in such a DHEA effect have already been provided and include:

- a protective effect on the vascular endothelium [28];
- the modulation of the Ca2+ activated potassium channel expression and activity [18];
- activation of the RhoA/Rho kinase signalling pathway [29];
- a decrease in vascular remodeling with activation of apoptosis and decrease in cellular proliferation via the inhibition of transcription factors such as hypoxia inducible factor (HIF1) or nuclear factor of activated T cell (NFAT) [30,31].

The excellent clinical tolerance of DHEA in general, and particularly regarding the stability of the respiratory status in the present study, must be underlined. Indeed, respiratory variables (forced expiratory volume in one second, vital capacity, PaO2, PaCO2, SaO2 and SvO2) remained unchanged after 3 months of treatment as shown in Table 4. In addition, the lung diffusing capacity for carbon monoxide used as a global marker of the lung function, increased significantly presumably as a consequence of the decrease in pulmonary hypertension [32]. This differs from results obtained with specific pulmonary vasodilators that potentially worsen the respiratory status [7–9]. For example, Prostacyclin and Bosentan have been evaluated in placebo-controlled studies and a decrease in arterial oxygenation was reported [7,8]. In two studies, Sildenafil did improve exercise and hemodynamic tolerance but no assessment of gas exchange was performed [33–35] whereas, more recently, a worsening in arterial oxygenation was reported in a prospective study including 20 patients [9].

In conclusion, we hereby show, for the first time in humans, that a 3-month DHEA treatment of PH-COPD patients improves both their clinical and hemodynamics status with an excellent overall as well as respiratory tolerance. Despite the limited number of patients and the open design of the study, the present proof of concept data open the way for multi-center double-blind placebo-controlled study to evaluate DHEA as a new therapy for PH-COPD patients.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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