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Evaluation of the Sildenafil Effects on Forced Expiratory Volume in One Second (Fev1) in Patients with Chronic Obstructive Pulmonary Disease (Copd)

KEYWORDS: Sildenafil; forced expiratory volume in one second (FEV1); chronic obstructive obstructive pulmonary disease(COPD)

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ABSTRACT *Background: sildenafil have been shown in small studies to decrease pulmonary arterial hypertension (PAH). Increased cGMP concentration results in pulmonary vasculature relaxation; vasodilation in the pulmonary bed and systemic circulation may occur.*

According to Sildenafil effects in pulmonary disease especially in PAH, this study was conducted to evaluate the safety and efficacy of Sildenafil as a rapid acting drug for treatment of COPD patients.

METHODS AND SUBJECTS

Twenty three patients suffering from stable COPD who referred to Rasoul-e-Akram Hospital, Tehran, Iran in 2008 participated in this prospective quasi-experimental trial. These 23 patients received single dose of 50mg oral sildenafil. FEV1 has been measured before and after drug administration.

The data were analyzed using SPSS v.16 software for Windows (SPSS Inc, Chicago, IL, USA). Parameters such as frequency, mean, mode and standard deviation (S.D.) were reported. Kolmogronov Smirnov (K.S) test was performed to evaluate normal distribution of the quantitative variables.

Results:

The results of analysis show that sildenafil significantly increase FEV1 from 1.29(SD=0.61) to 1.43(SD=0.77) (P<0.001).

The sex, pulmonary hypertension and smoking had not significant effect on changes of FEV1 before and after treatment with P value of 0.52, 0.062 and 0.935, respectively.

Also aforementioned factors had not significant effect on changes of respiratory symptoms before and after treatment with P value of 0.448, 0.200 and 0.382, respectively.

Conclusion:

The usage of Sildenafil in the improvement of COPD is better to be recommended after performing and reporting the results of phase II or III human trials with a greater sample size.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by partially reversible airflow obstruction caused by an inflammatory response to inhaled toxins, often cigarette smoke [1,2].COPD is a common condition with a high and continually increasing mortality. It is estimated that approximately 8 percent of all individuals have COPD [3].Prevalence is higher in men probably because men have a higher prevalence of smoking.

Pulmonary function tests (PFTs) are used to diagnose COPD, determine the severity of the airflow obstruction, and follow disease progression. The most important values measured are the FEV1 and the forced vital capacity (FVC) [4-7].

Pharmacotherapy for COPD is used to prevent and decrease symptoms (especially dyspnea), reduce the frequency and severity of exacerbations, improve health status, and improve exercise capacity [8] .The mainstays of drug therapy of COPD have been recommend by The Global Initiative for Chronic Obstructive Lung Disease (GOLD) are bronchodilators, primarily beta agonists and anticholinergics, and inhaled glucocorticoids, given alone or in combination depending upon the severity of disease and response to therapy[9-15].

It is also recognized that erectile dysfunction is common in

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COPD patient population [3] and many COPD patients are reluctant to engage in sexual activity because of the respiratory distress associated with this activity.

Sildenafil which is used in erectile dysfunction, enhances the effect of nitric oxide (NO) by inhibiting phosphodiesterase type 5 (PDE-5), inhibition of PDE-5 by sildenafil causes increased levels of cyclic guanosine monophosphate (cGMP). in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum [16].

sildenafil have been shown in small studies to decrease Pulmonary arterial hypertension (PAH) [17-19] . Inhibition of PDE-5 in smooth muscle of pulmonary vasculature where PDE-5 is responsible for the degradation of cGMP. Increased cGMP concentration results in pulmonary vasculature relaxation; vasodilation in the pulmonary bed and the systemic circulation (to a lesser degree) may occur.

For the first time, two patients with severe COPD and erectile dysfunction reported by Charan NB in 2001 [20] that their dyspnea improved when they took oral sildenafil for erectile dysfunction. Spirometry performed in these patients revealed an improvement in FEV1 by 24% and 12%.

Stanopoulos I et al. in 2007[21] report three cases of mechanically ventilated COPD patients who were intubated due to an exacerbation of their disease and who presented with repeated spontaneous breathing trial failures. Patients were given 50 mg of sildenafil through the nasogastric tube, under close monitoring of haemodynamic and ventilatory parameters. After sildenafil, pulmonary artery pressure, pulmonary artery occlusion pressure, the respiratory frequency to tidal volume ratio and the P(a)CO2-P(ET)CO2 (arterial minus end-tidal carbon dioxide pressure) decreased. Cardiac output increased in two of the patients, while all of them were successfully extubated.

In another study, Rietema H et al in 2008[22] showed that in a group of 15 COPD patients, neither stroke volume nor exercise capacity were improved by 3 months of sildenafil therapy.

Considering our literature review,we found just a few case report study with different results, therefore according to Sildenafil effects in pulmonary disease especially in PAH, this study was conducted to evaluate the safety and efficacy of Sildenafil as a rapid acting drug for treatment of COPD patients.

METHODS AND SUBJECTS

Study Desgn

Twenty three patients suffering from stable COPD who referred to Rasoul-e-Akram Hospital, Tehran, Iran in 2008 participated in this prospective quasi-experimental trial. These 23 patients received single dose of 50mg oral sildenafil. FEV1 has been measured before and after drug administration.

Participants

Twenty three patients with COPD, in the stable phase of the disease, participated in the study after giving them informed consent. The patients had to fulfill the American Thoracic Society (ATS) criteria for the diagnosis of COPD.

Inclusion criteria were: no recent pulmonary infection, no Myocardial Infarction(MI) in past month, stable phase of disease, no administration of other bronchodilator in past month and possibility of taking part in Spirometry test for two times;(We choose 23 subjects among patients had these criteria randomly). whereas patients with drug side effect, no tendency of taking part in the study and changing patient condition, so they couldn't tolerate 2 times of Spirometry test were excluded.

Intervention

Demographic variables were recorded.Patients continue their previous medications. FEV1and pulmonary symptoms were measured before and one hour after drug administration . The change in FEV1 was the primary outcome in our study to show bronchodilatory effect of the drug.

Data Analysis

The data were analyzed using SPSS v.16 software for Windows (SPSS Inc, Chicago, IL, USA). Parameters such as frequency, mean, mode and standard deviation (S.D.) were reported. The analyses were performed using statistical tests. Kolmogronov Smirnov (K.S) test was performed to evaluate normal distribution of the quantitative variables. To compare the differences between the values of continuous variables before and after treatment paired T-test was used a 5% probability of a type I error (two-tailed), and a power of 80% was considered in the analysis. All reported p-values are two-tailed. Moreover, the change of qualitative values of the pulmonary symptoms (before and after treatment) was evaluated using Chi-square test.

A 5% probability of a type I error (two-tailed), and a power of 80% were considered in the analysis. All reported p-values are two-tailed.

RESULTS

Twenty three patients were investigated in this study, 13 were males (56.5%) and 10 were females (43.5%). The mean age was 62.96 (SD=13.63) yr ranged between 43 to 88 years. The duration of disease was 3 month to 20 years with a mean of 8.88(SD=5.49) yr. Fifteen (65.2%) patients were cigarette smoker; five (21.7%) of them had a history of using cigarette less than 20pack/year, while others (43.5%) were heavy smokers (more than 20pack/year).four(17.4%) of cases had pulmonary hypertension.

Respiratory symptoms reduced in 43.5 %(n=10) and there was no change in56.5 %(n=13) after administration of sildenafil. We had not any patient with worsening of symptoms.

The results of analysis show that sildenafil significantly increase FEV1 from 1.29(SD=0.61) to 1.43(SD=0.77) (P<0.001).

The sex, pulmonary hypertension and smoking had not significant effect on changes of FEV1 before and after treatment with P value of 0.52, 0.062 and 0.935, respectively.

Also, the sex, pulmonary hypertension and smoking had not significant effect on changes of respiratory symptoms before and after treatment with P value of 0.448, 0.200 and 0.382, respectively.

DISCUSSION

In this study, we demonstrated that oral Sildenafil treatment significantly decreased FEV1 in COPD patients from 1.29 to 1.43 liters and also symptoms of patients reduced in 10(43.5 %) patients but in 13(56.5%)patients the symptoms didn't changed.

To date, only a few studies have evaluated the efficacy of sildenafil therapy in in COPD patients including two case reports and a case series evaluation [21-22].

Charan NB 2001 reported two cases,in one case 1 hour after receiving oral sildenafil, 100 mg. His FVC improved from 2.71 L to 3.73 L (38% increase), and his FEV1 improved from 0.96 L to 1.19 L (24% increase).

And in other case 1 h after receiving sildenafil, 50 mg (his usual dose). His FVC changed from 2.86 to 2.98 L (4% increase), and his FEV1 changed from 0.67 to 0.75 L (12% increase).

Although improvement in airway function with sildena-

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fil has not been reported previously, this association may have some scientific basis. Sildenafil is a selective inhibitor of cyclic guanosine 3′,5′-monophosphate-specific phosphodiesterase (PDE) type 5, which is the predominant enzyme that metabolizes cyclic guanosine 3′,5′-monophosphate[23]. Isoenzyme-selective PDE inhibitors that have been known to cause bronchodilation are usually related to PDE type 3 and PDE type 4 types, but recently PDE type 5 inhibition also has been implicated in reversing bronchoconstriction[24]. Therefore, it is possible that oral sildenafil therapy may improve airway functions by causing airway smooth muscle relaxation.

In conclusion, it appears that sildenafil does not have any deleterious effect on pulmonary functions in patients with COPD. In fact, in certain patients with COPD who also experience erectile dysfunction, sildenafil may improve not only the erectile dysfunction but may also have a beneficial effect on postcoital respiratory distress, a unique but perhaps an important additive benefit of the drug in this patient population.

It is difficult to draw certain conclusions from this because of the following limitations: (1) the observation was made in only 23 patients; (2) a placebo was not used; (3) patients especially females refused using Sildenafil because of social problem (sildenafil known as sexual dysfunctin drug).

However, a systematic and placebo-controlled study will be required to confirm this hypothesis. And the usage of Sildenafil in the improvement of COPD is better to recommend after performing and reporting the results of phase II or III human trials with a greater sample size.

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