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Does sildenafil improve ventilatory function in asthmatic subjects?

Case report

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Sildenafil is well known selective phosphodiesterase-5 (PDE-5) enzyme inhibitor that is used extensively in erectile dysfunction in males. The effect of sildenafil is mediated through raising the tissue level of the second messenger cyclic guanosine monophosphate (cGMP) leading to relaxation of smooth muscle [1] through reduction of intracellular [Ca^{2+}] and downregulation of contractile apparatus [2]. The reduction of intracellular [Ca^{2+}] is through inhibition of Ca^{2+} influx [3] and decreasing Ca^{2+} release from the endoplasmic reticulum by blocking Ca^{2+} channels [4]. PDE-5 is found in high concentrations in the corpus cavernosum and in pulmonary artery smooth muscle, and therefore its inhibition leads to an increase in penile blood flow and a decrease in pulmonary vascular resistance [5]. Levels of cGMP in smooth muscle is also increased by nitric oxide (NO), which is formed from L-arginine through the actions of different types of NO synthase. NO acts a vasodilator, neurotransmitter and inflammatory mediator in human airways [6]. It relaxes tracheal smooth muscle [7] and decreases methacholine-induced bronchoconstriction in experimental animals [8]. Turner *et al.* [9] presented supporting evidence for a role of NO in airway dilatation by demonstrating that an NO-donating compound potentiates the effects of a β_2-adrenoceptor agonist.

Toward *et al.* [10] showed that sildenafil pretreatment, in a dose equivalent to the human oral dose, inhibits the airway hypersensitivity and leukocyte influx in conscious guinea pig models. In addition, Wang *et al.* [11] demonstrated that sildenafil could reduce airway inflammation and mucus production in a rat model. Only one case study published in 2001 showed that some improvement in lung function in two chronic obstructive pulmonary disease (COPD) patients using sildenafil [12]. Here, we present another case report to support the beneficial effect of sildenafil on lung function.

Case presentation

A male, 42-year-old dry-cleaning worker known to have asthma (forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio 54%). He had participated in our study on the effects of phosphodiesterase enzyme inhibition on lung function. The written consent of the patient was obtained and the research was approved by the research committee at Jordan University of Science and Technology (Irbid, Jordan). The patient had been off bronchodilators for ≥3 days before the test. Spirometry was performed before taking a 50-mg sildenafil tablet and 2 h after taking the drug. The test was repeated on six occasions separated by 5 days. Three spirometry attempts before and after the drug were performed on each visit and the mean of the three readings was taken. The value before taking the drug was considered as the

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baseline value. The percentage changes in pulmonary function test were recorded as the value after taking sildenafil minus the baseline value over the baseline value. FEV_1, forced expiratory flow at 25–75% of FVC ($FEF_{25-75\%}$) and peak expiratory flow rate (PEFR) values improved after taking the drug (table 1). The average increase in FEV_1, $FEF_{25-75\%}$ and PEFR values 2 h after taking sildenafil tablet were 14%, 26% and 13%, respectively. The average increment in FEV_1, $FEF_{25-75\%}$ and PEFR are 304 mL, 450 mL·s^{-1} and 526 mL·s^{-1}, respectively. The changes in FEV_1 after taking the drugs over six visits are shown in figure 1. At all visits, the FEV_1 values had increased after taking the drug.

Table 1 *Pulmonary function test parameters before and 2 h after taking 50 mg sildenafil*

Parameter	Before taking 50 mg sildenafil (baseline value)	2 h after taking 50 mg sildenafil
FEV_1 L	2.22±0.39	2.54±0.36*
$FEF_{25-75\%}$ L	1.25±0.32	1.53±0.36*
PEFR L·s^{-1}	4.96±0.80	5.59±0.61*

Data are presented as mean±SD. *: p<0.05.

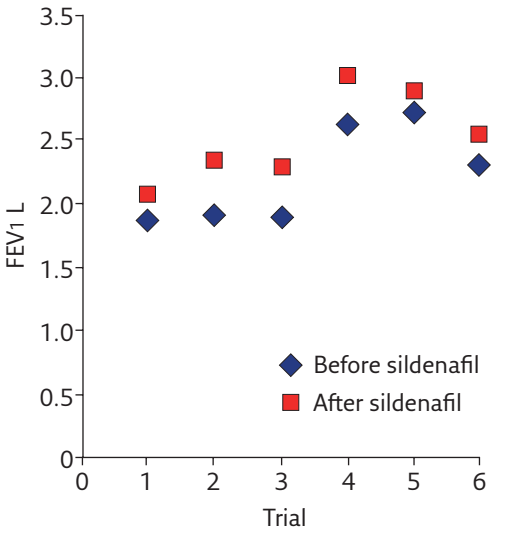

Figure 1 *Mean FEV_1 over six visits. Each point represents the mean of three attempts.*

Task 1
What are the criteria for reliable FVC recording?

Task 2
How could you determine the airway obstruction reversibility after bronchodilator treatment and did sildenafil treatment reverse obstruction in this patient?

Task 3
Compared with FVC, vital capacity in normal subject is
a. slightly higher
b. of same value
c. slightly lesser
d. greatly higher
e. greatly lesser

Answer 1
A reliable spirometry recording must meet these criteria [13]:

1 expiration must be maintained for ≥6 s
2 the volume–time curve must reach a plateau
3 a series of at least three forced expiratory curves that are within 200 mL of each other, have an acceptable start of test, and are free of artefacts and abnormalities such as a cough

Answer 2
Determination of the reversibility of airway obstruction is based on increased FEV_1 value after treatment. An increase of >12% and >200 mL is considered as a positive sign for reversibility of the obstruction [14]. Since FEV_1 was increased by 304 mL (14% increase compared with before treatment), we can therefore assume that sildenafil succeeded in reversing the obstruction.

Answer 3
d. slightly higher

Discussion

Relaxation of smooth muscle can be achieved by increasing its levels of cGMP, which can be achieved either by sildenafil through its action on the enzyme that destroys it or by NO through activation of soluble guanylate cyclase enzyme, which catalyses the formation of cGMP from guanosine triphosphate. Since airway smooth muscle uses NO as neurotransmitter at the ends of nonadrenergic, noncholinergic fibres [15], it is logical to assume that sildenafil has bronchodilator effects as it decreases the destruction of cGMP produced through action of NO on airway smooth muscle. It is postulated that the bronchodilation effect of NO is more obvious in large airways and has only a slight action on small airways [16].

Erectile dysfunction is common in COPD patients who have ceased sexual activity due to worsening of their pulmonary symptoms and erectile impotence. Although it is hard to draw solid conclusions from single case, our data suggest some beneficial effect of sildenafil on lung function. It is difficult to say at present that the improvement in lung function parameters in this case is due to natural variability in pulmonary function or due to a genuine effect of sildenafil. This case report has the same limitations mentioned in case report described previously [12]. The scientific basis for using sildenafil in airway flow limitation comes from the fact that cGMP mediates relaxation of airway smooth muscle *via* "classic" protein kinase/protein phosphorylation cascade mechanisms and since sildenafil increases the tissue levels of cGMP, so it has the potential to relieve the bronchoconstriction in asthmatic patients by causing airway smooth muscle relaxation or reducing the inflammatory changes associated with exaggerated airway responsiveness. Therefore, it would very reasonable to find whether bronchoconstriction amongst users of sildenafil are improved or not in a large-scale clinical study. This case report supports a previous report [12].

The moderate improvement in lung function parameters in our case may be attributed to the dilatory effect of increased levels of cGMP on the smooth muscle of blood vessels supplying the airway. This vasodilatation may lead to oedema and increased mucus production, and this may reduce the airway diameter, thus decreasing the bronchodilatory effect of increased levels of cGMP on bronchial smooth muscle. Since ventilatory changes in asthmatic patients are attributed to changes involving mainly small airways, then one can explain the moderate effect of sildenafil on airways in this asthmatic patient by there being less cGMP generated from NO in small airways compared to large airways [16].

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Conflict of interest

None declared.

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