Sildenafil Improves Exercise Capacity in Patients with Chronic Heart Failure

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SUMMARY

Background
Phosphodiesterase type 5 inhibitors, as sildenafil, are moderate vasodilators widely used for erectile dysfunction. The evidence currently available establishes that they are potentially useful to treat other conditions like pulmonary hypertension, endothelial dysfunction and chronic heart failure.

Objective
To evaluate whether sildenafil is useful to improve exercise capacity compared to placebo in patients with chronic heart failure in functional class II-III.

Material and Methods
A total of 70 patients with chronic heart failure of any etiology, excluding valvular heart disease, were randomly selected. All patients were receiving optimal medical treatment. Patients were included if they had a left ventricular-diastolic diameter of 55 mm, an ejection fraction <35%, systolic blood pressure >90 mm Hg. Patients with anemia, an indication of surgery due to any cause, and those unable to undergo a 6-minute walk test were excluded from the study. After the 6-minute walk test, the patients were randomly assigned to receive 50 mg of sildenafil (sildenafil group) or placebo (placebo group); each group had 35 patients. A second 6-minute walk test was performed 2 hours after the drug was administered. The following variables were evaluated before and after each test: systolic blood pressure, heart rate and the distance walked in meters in each test.

Results
General characteristic, placebo group versus sildenafil group: men: 74% vs. 88%, ischemic dilated cardiomyopathy: 71% vs. 77%, functional class II: 37% vs. 34%, functional class III: 63% vs. 66%, age: 68±10 vs. 68±12 years, ejection fraction: 26.5%±7.8% vs. 26.5%±6.5%, left ventricular end-diastolic diameter: 65±6 vs. 66±9 mm (all p = ns). Before the first 6-minute walk test, the following variables were measured in the placebo versus the sildenafil group: systolic blood pressure: 115±15 vs. 115±21 mm Hg; diastolic blood pressure: 71±10.5 vs. 68±13 mm Hg (both p = ns); heart rate: 74±13 vs. 64±6 (p <0.001). After the first test and before drug administration: systolic blood pressure: 126±20 vs. 133±26 mm Hg, diastolic blood pressure: 68±11 vs. 72±15 mm Hg; heart rate 84±2 vs. 80±9 (all p = ns). Before the second test and after drug administration, placebo versus sildenafil: systolic blood pressure: 112±14 vs. 95±18 mm Hg; diastolic blood pressure: 69±8 vs. 57±12 mm Hg (both p <0.001); heart rate: 73±11 vs. 75±10 (p = ns). Finally, after the second walk test: systolic blood pressure: 123±17 vs. 115±26 mm Hg (p <0.05), diastolic blood pressure: 65±7 vs. 60±12 mm Hg (p <0.02) and heart rate: 84±13 vs. 86±12 (p = ns). The incidence of headache was 11% (4 patients) in the sildenafil group and 0% in the placebo group. The incidence of headache reported in the group of patients with heart failure in functional class II-III under optimal medical therapy, sildenafil improved exercise capacity compared to placebo.

Conclusions
In patients with heart failure in functional class II-III under optimal medical therapy, sildenafil improved exercise capacity compared to placebo.
BACKGROUND

Phosphodiesterase family (PDE) comprises a group of enzymes that hydrolyze adenosine and guanosine cyclic nucleotides. Nitric oxide activates guanylyl and adenylyl cyclases, the enzymes that degrades guanosine triphosphate and adenosine triphosphate and converts them to cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP). Both cyclic nucleotides act as second messengers. cGMP promotes decrease in intracellular calcium concentrations, leading to smooth muscle relaxation. (1) Sildenafil, a selective inhibitor of type 5 phosphodiesterase (PDE5), produces coronary artery vasodilation and was originally investigated to determine its potential use as an anti-ischemic agent. Currently, sildenafil is used for the treatment of erectile dysfunction. The evidence available establishes that it is potentially useful to treat other conditions like pulmonary hypertension, endothelial dysfunction and chronic heart failure (CHF). (1-3)

Exercise capacity in CHF is determined by several central and peripheral mechanisms. Thus, pulmonary resistance and right ventricular performance influence exercise capacity and prognosis of patients with CHF and right ventricular systolic dysfunction. (5-9) Around 68% to 78% of patients with severe left ventricular dysfunction have pulmonary hypertension that produces right ventricular dysfunction. In addition, pulmonary hypertension is considered an important predictor of low functional capacity in CHF. (5, 6, 10, 11)

Endothelial dysfunction also plays a role in CHF and is associated with the clinical presentation and prognosis. (12-15) Endothelial dysfunction is an abnormal response of the endothelium that reduces the bioavailability of vascular nitric oxide and impairs vasodilation. (16) The inhibition of 5-PDE with sildenafil has proved to be useful in different condition with impaired endothelial function and vascular tone. (17) This favorable effect is partially mediated by increased bioavailability of nitric oxide in the vascular bed. (18) The loss of vasodilator capacity induces changes which increase peripheral vascular resistance, and thus contributes to reducing cardiac performance, producing changes in pulmonary hemodynamics that lead to the development of pulmonary hypertension. (12) Finally, in CHF vasoconstriction generates elevation in aortic impedance which, in turn, increases left ventricular afterload, wall stress and oxygen uptake. The inhibition of PDE5 improves cardiac performance in patients with CHF, probably due to reduction in afterload components: peripheral resistance, stiffness of the aorta and great vessels and peripheral wave reflection. Recent publications have reported improvement in exercise capacity in patients with CHF after the administration of a single dose of sildenafil. (19-23)

The goal of the present study was to determine the effect of a single dose of 50 mg of sildenafil on exercise capacity compared to placebo, evaluated by a 6-minute walk test, in patients with New York Heart Association (NYHA) functional class (FC) II-III chronic heart failure.

MATERIAL AND METHODS

We conducted a randomized, double-blind, controlled trial to evaluate whether a single dose of 50 mg of sildenafil is useful to improve exercise capacity compared to placebo in patients with CHF.

Patients were enrolled in a single center and were randomly assigned to sildenafil or placebo in a double-blind fashion. The goal of the study was to evaluate whether sildenafil, in a single dose of 50 mg, improves the physical performance of patients with CHF.

CHF patients with NYHA FC II-III were prospectively and consecutively enrolled. All patients gave their consent to be included in the study and signed an informed consent form. All patients had been attending the heart failure clinic for at least 6 months. All patients were receiving angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), beta blockers and spironolactone in optimal or maximal tolerated dose. Each participant underwent a thorough physical examination, laboratory tests, 2D-echocardiography and radionuclide ventriculography to determine ejection fraction. Myocardial perfusion tests were ordered to patients with a history of ischemic cardiomyopathy to rule out the presence of ischemia that might benefit from revascularization treatment.

Patients were included if they were > 21 years, had left ventricular-diastolic diameter (LVDD) > 55 mm, ejection fraction (EF) < 35% systolic blood pressure >90 mm Hg.

Patients were excluded from the study if they were under treatment with nitrates, had intolerance to sildenafil, an indication of surgery due to any cause, were waiting for revascularization surgery, had anemia, valvular heart disease or hypertrophic cardiomyopathy, or were unable to undergo a 6-minute walk test. A total of 178 patients were attending the heart failure clinic; 70 were eligible to be included in the study. Before the test, and after a 15-minute rest period, blood pressure, heart rate and oxygen saturation were controlled by the same operator. The patients were
RESULTS

After unblinding, two groups were established. When baseline characteristics of patients were compared (Table 1) there were no differences between both groups.

There were more men than women; mean age was 68 years and 2/3 of patients were in FC III. Heart failure was more frequently due to ischemic heart disease and mean EF was 26.5%. All the participants were receiving ACEIs or ARBs, beta blockers and spironolactone in optimal or maximal tolerated dose. The clinical variables controlled in both groups before and after the initiation of the 6 minute-walk test are shown in Table 2. No medication was administered during the test. Differences in systolic and diastolic pressure before the first walk; differences in heart rate were observed. After the first walk, the three variables presented changes in both groups; however there were no significant differences between both groups.

Table 3 describes the clinical variables after the randomization and the administration of the corresponding drug, before and after the second 6-minute walk test.

After the administration of sildenafil, and with the patient at rest, systolic and diastolic blood pressure presented significant reduction in the sildenafil group without changes in heart rate. After the second walk, heart rate increased in both groups without significant differences. On the contrary, systolic and diastolic blood pressure decreased significantly in the sildenafil group compared to the placebo group.

Table 4 shows the average walked, in meters, for each group. Patients in the sildenafil group walked 222 ± 69 and 313 ± 76 meters in the first and second walk, respectively, with a difference of 91 ± 19 meters. The placebo group walked ± 242 and 242 ± 67 meters in the first and second walk, respectively; the difference was 9 ± 5 meters. There were no significant differences in the distance walked by each group in the first test; however, the distance walked by patients in the sildenafil group in the second test was significantly greater compared to the control group.

Two hours after the second walk patients left the hospital. None of the participants complained of major
DISCUSSION

Previous studies have reported an average blood pressure reduction of 6 to 8 mm Hg in healthy subjects in the supine position two hours after the administration of 50 mg of sildenafil. This reduction is not greater in the erect position, even with greater dose. (24, 25) Blood pressure reduction produces reflex tachycardia. (26, 27)

In patients with FC II chronic heart failure, a single dose of sildenafil improved significantly the outcomes of six-minute walk test on treadmill, compared to placebo (23) These results are similar to other study using fixed dose of 50 mg/day during 6 weeks, which reported improvement on functional capacity without significant changes in blood pressure or heart rate. (28)

Lewis et al. demonstrated that, in patients with CHF, a single dose of sildenafil improves exercise capacity. (21) Another study by the same group included patients with CHF and pulmonary hypertension, and reported that treatment with sildenafil for 12 weeks increased the distance in meters walked during the 6-minute walk test compared to placebo. (29)

Recently, Behling et al. showed that the administration of sildenafil for 4 weeks improved the functional capacity compared to placebo. (30)

Several mechanisms may be involved with the improvement in functional capacity in these patients. Sildenafil increases right ventricular ejection fraction, probably due to a reduction in afterload as a consequence of decreased pulmonary vascular resistance. (31-33) Probably, improvement in right ventricular function during exercise increases stroke volume due to increased left ventricular filling volume. The improvement of the vasodilator capacity of sildenafil might reduce pulmonary and
systemic vascular resistance and thus increase cardiac performance. (12-16) It is also possible that a reduction in left ventricular overload due to decreased systemic vascular resistance increases contractility and left ventricular systolic stroke. (22)

We have demonstrated that a single dose of 50 mg of sildenafil improves exercise capacity of patients with NYHA FC II-III CHF evaluate by the six-minute walk test. Sildenafil was well tolerated and was associated with minimal adverse effects; however, compared to placebo, it produced significant reduction of systolic and diastolic blood pressure without increasing heart rate. Yet, these variable presented normal changes during exercise.

As opposed to previous reports, we found a pronounced increase in the distance walked in six minutes - mean distance: 90 meters - in the sildenafil group. Probably, this might be due to the fact that we included more patients in FC III who walked a shorter distance in the first test compared to patients in other studies. Left ventricular function might have been more deteriorated in our patients.

Clinical implications
Few particular subgroups of patients with CHF might beneficiate from inhibition of PDE5; for example, patients with limited exercise capacity despite optimal medical treatment. In addition, PDE5 inhibition might be used before cardiac resynchronization therapy or when this therapy does not improve symptoms or functional class. Patients on waiting list for a heart transplant might also beneficiate from this treatment. These potential indications should be examined with studies designed to demonstrate a maximal benefit.

Study limitations
We used two-dimensional echocardiography without Doppler examination to measure cardiac chambers; thus, we did not evaluate pulmonary pressure. Therefore, we do not know if the effect obtained in the active group corresponds to patients with pulmonary hypertension. Although our study includes a small number of patients, the magnitude of the difference makes it highly reliable. These results need to be confirmed by further investigations including a greater number of patients.

CONCLUSIONS
In patients with CHF in FC II-III, the administration of sildenafil produces a significant improvement in exercise capacity compared to placebo. In addition, the rate of adverse effects was very low.

RESUMEN
El Sildenafil mejora la capacidad de ejercicio en pacientes con insuficiencia cardiaca crónica

Antecedentes
Los agentes inhibidores de la fosfodiesterasa 5, como el silde
nafil, son vasodilatadores moderados ampliamente utilizados para el tratamiento de la disfunción eréctil. En la actualidad, la evidencia disponible establece su potencial aplicación en otras patologías, como la hipertensión pulmonar, la disfunción endotelial y la insuficiencia cardiaca crónica.

Objetivo
El presente estudio fue diseñado para comprobar si la ad
ministración de sildenafil en pacientes con insuficiencia cardiaca crónica en clase funcional II-III mejora la capacidad de ejercicio en comparación con placebo.
Material y métodos
Se seleccionaron en forma aleatoria 70 pacientes portadores de insuficiencia cardiaca crónica de cualquier etiología, excepto valvulares, todos con tratamiento óptimo. Para su inclusión en el estudio, los pacientes debían tener un diámetro diastólico ventricular izquierdo > 55 mm, una fracción de eyeción < 35% y una presión arterial sistólica > 90 mm Hg. Se excluyeron los que se encontraban anécticos, aquellos con indicación de cirugía por cualquier causa o los que por diversos motivos no pudieran realizar una caminata de seis minutos. Luego de una caminata de seis minutos fueron aleatorizados para recibir 50 mg de sildenafil o placebo, conformándose dos grupos, placebo y sildenafil, ambos con 35 participantes. Luego de 1 hora de la ingestión de las drogas se realizó una nueva caminata de seis minutos. Antes y después de cada caminata se controlaron las siguientes variables: presión arterial sistólica, diastólica y frecuencia cardíaca; se registraron también los metros caminados en cada prueba.

Resultados
Características generales, grupo placebo versus grupo sildenafil: hombres: 74% vs 88%, etiología isquémico-necrótica: 71% vs 77%, clase funcional II: 37% vs 34%, clase funcional III: 63% vs 66%, edad: 68 ± 10 vs 68 ± 12 años, fracción de eyeción: 26,5% ± 7,8% vs 26,5% ± 6,5%, diámetro diastólico ventricular izquierdo: 65 ± 6 vs 66 ± 9 mm (todas p = ns). Las variables del grupo placebo versus sildenafil antes de la primera caminata fueron: presión arterial sistólica: 115 ± 15 vs 115 ± 21 mm Hg y diastólica: 71 ± 10,5 vs 68 ± 13 mm Hg (ambas p = ns) y frecuencia cardíaca: 74 ± 13 vs 64 ± 6 (p < 0,001). Luego de la primera caminata y antes de la administración de las drogas: presión arterial sistólica: 126 ± 20 vs 133 ± 26 mm Hg, diastólica: 68 ± 11 vs 72 ± 15 mm Hg y frecuencia cardíaca 84 ± 2 vs 80 ± 9 (todas p = ns). Antes de la segunda caminata y luego de la administración de las drogas, grupo placebo versus sildenafil: presión arterial sistólica: 112 ± 14 vs 95 ± 18 mm Hg, diastólica: 69 ± 8 vs 57 ± 12 mm Hg (ambas p < 0,001) y frecuencia cardíaca: 73 ± 11 vs 75 ± 10 (p = ns). Finalmente, luego de la segunda caminata: presión arterial sistólica: 123 ± 17 vs 115 ± 26 mm Hg (p < 0,05), diastólica: 65 ± 7 vs 60 ± 12 mm Hg (p < 0,02) y frecuencia cardíaca: 84 ± 13 vs 86 ± 12 (p = ns). Cuatro pacientes (11%) en el grupo sildenafil presentaron cefalea y ninguno en el grupo placebo. No se registraron eventos mayores. El grupo sildenafil caminó 222 ± 69 metros antes y 313 ± 76 luego de la administración de la droga; la diferencia en metros fue de 91 ± 19. El grupo placebo caminó 233 ± 67 metros antes y 242 ± 67 luego de la administración de la droga; la diferencia en metros fue de 9 ± 5. Al comparar estos resultados, la diferencia en metros recorridos resultó significativa a favor del grupo sildenafil: 91 ± 19 vs 9 ± 5 (p < 0,0001).

Conclusiones
En pacientes con insuficiencia cardiaca en clase funcional II-III bajo tratamiento óptimo, el sildenafil mejoró la capacidad de ejercicio en comparación con placebo.

Palabras clave > Insuficiencia cardiaca - Ejercicio - Capacidad residual funcional

BIBLIOGRAPHY


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Competing interests
None declared.