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Phosphodiesterase Type 5 Inhibitors Can Alleviate Exercise-Induced Skeletal Muscle Ischemia in Males with Muscular Dystrophy

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Phosphodiesterase Type 5 Inhibitors Can Alleviate Exercise-Induced Skeletal Muscle Ischemia in Males with Muscular Dystrophy

Abstract

Background: Muscular Dystrophy (MD) is a progressive X-linked muscular wasting disease. Glucocorticoids are currently being used to prolong ambulation for 2 to 3 years, but have failed to alleviate muscle ischemia and prevent muscle injury. The muscle ischemia occurs in these patients as a result of mutations in the gene coding for the protein dystrophin important in the protective mechanism otherwise known as functional sympatholysis. Studies on mice deficient in dystrophin found restoration of this mechanism with the use of phosphodiesterase type 5 (PDE5) inhibitors. The purpose of this review was to investigate whether PDE5 inhibitors could alleviate exercise-induced skeletal muscle ischemia in human patients with MD.

Methods: An exhaustive search of MEDLINE-Ovid, Web of Science, MEDLINE-PubMed, and Clinical Key was performed using keywords: sildenafil, tadalafil, PDE5 inhibitors, and muscular dystrophy. Studies were screened for eligibility criteria which included only human studies published in English. Both studies were assessed using the GRADE approach for quality of evidence.

Results: Two studies were included in this systemic review. One was a case-control study to establish functional sympatholysis is impaired in patients with Duchenne MD and with the use of both tadalafil and sildenafil where restoration occurred indistinguishably from healthy controls. The other study performed a case-control initially to establish impaired functional sympatholysis in patients with Becker MD followed by a randomized double-blind placebo controlled crossover trial to test whether tadalafil restored this mechanism. Results were similar in that functional sympatholysis was restored indistinguishably from healthy controls.

Conclusion: PDE5 inhibitors restored functional sympatholysis in all but one patient across both studies. Despite the small sample sizes, very little variability existed across study results leading to receive a moderate level of quality of evidence based on the GRADE approach. These studies were only single-dose trials therefore the need for future studies is needed to assess whether these positive findings will be sustained upon chronic administration. Authors state longer term studies are in progress to assess whether the administration of PDE5 inhibitors can slow disease progression.

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Phosphodiesterase Type 5 Inhibitors Can Alleviate Exercise-Induced Skeletal Muscle Ischemia in Males with Muscular Dystrophy

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Biography

Becky Theisen is a native of Minnesota where she majored in Exercise Science at the University of St. Thomas. While there she was an All Conference basketball player and an All American sprinter in track & field. After college she coached high school basketball and track, worked at a local winery and became a nursing assistant in efforts to gain health care experience in order to apply for Physician Assistant school. She is currently attending Pacific University in Oregon.

Abstract

Background: Muscular Dystrophy (MD) is a progressive X-linked muscular wasting disease. Glucocorticoids are currently being used to prolong ambulation for 2 to 3 years, but have failed to alleviate muscle ischemia and prevent muscle injury. The muscle ischemia occurs in these patients as a result of mutations in the gene coding for the protein dystrophin important in the protective mechanism otherwise known as functional sympatholysis. Studies on mice deficient in dystrophin found restoration of this mechanism with the use of phosphodiesterase type 5 (PDE5) inhibitors. The purpose of this review was to investigate whether PDE5 inhibitors could alleviate exercise-induced skeletal muscle ischemia in human patients with MD.

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Keywords: PDE5 inhibitors, tadalafil, sildenafil, muscular dystrophy

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List of Abbreviations

MD.....	muscular dystrophy
DMD.....	Duchenne muscular dystrophy
BMD.....	Becker muscular dystrophy
nNOS μ	neuronal nitric oxide synthase
NO.....	nitric oxide
PDE5.....	phosphodiesterase
cGMP.....	cyclic guanosine 3'5'-monophosphate
FDA.....	Federal and Drug Administration
mdx.....	X-linked muscular dystrophy
MVC.....	maximum voluntary contraction
LBNP.....	lower body negative pressure
TLS.....	total labile signal

Phosphodiesterase Type 5 Inhibitors Can Alleviate Exercise-Induced Skeletal Muscle Ischemia in Males with Muscular Dystrophy?

BACKGROUND

Muscular dystrophy (MD) is a progressive X-linked muscle wasting disease for which there is no treatment.^{1,2} It often culminates in a loss of ambulation, cardiac involvement such as cardiomyopathy and respiratory insufficiency due to weakening of the inspiratory and expiratory muscles.³ Although glucocorticoids have been found to be helpful in prolonging ambulation for 2 to 3 years and temper cardiac decline in the second decade of life, they cause well-known side-effects which are intolerable to 25% of patients.^{1,2} There are many types with Duchenne muscular dystrophy (DMD) being the most common affecting approximately 1 in every 3000 live births.³ With this many people affected it is surprising the only options for treatment is to delay complications by a few years.⁴

The two types of MD discussed in this review are DMD and Becker muscular dystrophy (BMD) in which the latter is a less severe form, but still debilitating nonetheless. These patients have a mutation in a gene encoding for a cytoskeletal protein dystrophin resulting in a deficiency.⁵ DMD patients do not have this protein at all whereas it is reduced in patients with BMD. With dystrophin deficiency, the muscle sarcolemma is destabilized and the muscle fibers are susceptible to physical damage with repeated contraction.⁶ When healthy skeletal muscle is subjected to exercise, dystrophin targets a protein called neuronal nitric oxide synthase (nNOS μ) to the sarcolemma which derives the nitric oxide (NO) necessary to attenuate local α -adrenergic vasoconstriction for optimal muscle perfusion. This protective mechanism is termed functional sympatholysis and was found to be absent in boys with MD causing functional muscle ischemia.⁷

In mice, many features of the dystrophin phenotype can be improved by multiple strategies that boost NO signaling including phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil or tadalafil.⁸ These PDE5 inhibitors which prolong the half-life of cyclic guanosine 3'5'-monophosphate (cGMP)—the downstream target of NO in vascular smooth muscle—were shown to alleviate muscle ischemia, injury and fatigue, after a brief bout of exercise in the X-linked muscular dystrophy (mdx) mice⁹ as well as prolong survival of dystrophin-deficient zebrafish.¹⁰ Thus the NO-cGMP pathway constitutes a putative new drug target for DMD. [Nelson] Despite these positive findings in animals, little research has been done on PDE5 inhibitors on human patients with muscular dystrophy.

If PDE5 inhibitors can alleviate skeletal muscle ischemia it may lead to preserving dystrophic skeletal muscle and slow disease progression.⁴ Hence the following clinical question was formed for this systematic review: can PDE5 inhibitors alleviate exercise-induced ischemia in patients with MD?

METHODS

An exhaustive literature search was done using the databases MEDLINE-Ovid, Web of Science, MEDLINE-PubMed, and Clinical Key. The following key terms were used: “sildenafil,” “tadalafil,” “PDE5 inhibitors,” and “muscular dystrophy.” The search was limited to English and human studies only. The studies were then assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.¹¹

RESULTS

The above search initially yielded 37 articles. After applying eligibility criteria, a total of 14 articles were reviewed for relevancy. Two articles addressed the clinical question, including one case-control study [Nelson] and one random double-blind placebo-controlled crossover trial.¹² (See Table 1.)

Nelson et al

This was a case-control study⁴ to investigate PDE5 inhibitors on exercise-induced skeletal muscle ischemia in males with DMD. Ten boys aged 8-13 years old with a known diagnosis of DMD were compared to 10 healthy boys. Both cases and controls were excluded if they had a history of hypertension, diabetes mellitus, heart failure by history or physical examination; left ventricular ejection fraction <50%; required ventilator support; or had any contraindications to PDE5 inhibitors. Both cases or and controls were well matched for age, body mass index, blood pressure, and left ventricular ejection fraction. As expected, in patients with DMD resting heart rate was higher and maximum voluntary contraction (MVC) which represents grip strength was lower. These baseline characteristics were compared using student t tests for both the patients and controls. A separate table listed baseline characteristics about each of the 10 DMD patients including their current glucocorticoid medication which were continued throughout the study.⁴

To measure exercise-induced attenuation of reflex vasoconstriction (i.e. functional sympatholysis) the lower body negative pressure (LBNP) was 1) applied at rest and then 2) superimposed on mild rhythmic handgrip at 20% MVC. When LBNP was superimposed on handgrip in healthy controls, the reflex decrease in muscle oxygenation was attenuated indicating

functional sympatholysis. In contrast, no attenuation was seen in DMD patients indicating functional muscle ischemia.⁴ (See Figure 1.)

Next, only the patients with DMD participated in the PDE5 dose-finding study. Patients received .5 mg/kg (not to exceed 20 mg) orally of either sildenafil or tadalafil randomly on day 1, followed by 1.0 mg/kg (not to exceed 40 mg) orally on day 2. This was an open-label crossover design with a 2-week washout period before crossover (accounting for the 17.5 hour elimination half-life of tadalafil). Experiments were performed 1 hour after administration of sildenafil or 3 hours after administration of tadalafil to match the expected peak blood levels. Patients were asked about potential side effects such as facial flushing and penile erections in addition to being monitored for elevations in blood pressure throughout the study visits.⁴

The primary outcome was a 50% restoration of functional sympatholysis assessed by comparing percent total labile signal (%TLS) at rest vs. the decrease during the handgrip exercise. TLS was calculated by inflating an arm cuff to suprasystolic pressure to occlude the forearm circulation and produce a maximal decrease in muscle oxygenation. With the .5 mg/kg dose of tadalafil, the reflex decrease in muscle oxygenation attenuated in a response indistinguishable from normal (p =not significant vs. healthy controls). The 1.0 mg/kg dose caused a super-normal attenuation indicating tadalafil restored functional sympatholysis in boys with DMD in a dose dependent manner. (See Figure 2.) The results were confirmed with sildenafil in a subset of patients ($n=6$).⁴ (See Figure 1 and 2.)

The study had several limitations including a small sample size and an open-label design however the outcome was measured in an objective manner. The findings do not address whether restored sympatholysis will preserve dystrophic skeletal muscle over time and hence slow disease progression. Authors state multicenter clinical trials have been designed to determine

whether chronic daily tadalafil can preserve muscle function in patients with DMD was suggested.⁴

Martin et al

This was a randomized double-blind placebo-controlled crossover trial¹² to determine if tadalafil would restore functional sympatholysis in muscles of patients with BMD. Of 15 patients screened for eligibility, five males were excluded: two were too weak to perform handgrip, one had reduced left ventricular ejection fraction, one had hypertension, and one did not have BMD by mutational analysis. No patients were on nocturnal support. A case-control study was initially performed in 10 BMD patients ranging from 18-55 years old and seven age-matched healthy male controls to assess exercise-induced attenuation of reflex sympathetic vasoconstriction (i.e. functional sympatholysis). Reflex vasoconstriction was induced by simulated orthostatic stress and measured as the decrease in forearm muscle oxygenation at rest and while performing handgrip exercises represented by %TLS. Once it was found that reflex vasoconstriction was defective in 9 out of the 10 patients with BMD they began the double-blind randomized placebo-controlled crossover trial.¹²

The crossover design included a two-week washout period to account for the 17.5 hour elimination half-life of tadalafil. The double-blind technique was done by the research pharmacist who placed tadalafil tablets or lactose powder in opaque capsules to conceal the treatment from the patients and investigators. Patients received 20 mg tabs orally of either drug or placebo randomly three hours before measurement of functional sympatholysis. It was found with a single oral 20 mg dose of tadalafil, normal blood flow regulations was fully restored in 8 of the 9 patients with initially abnormal regulation. Furthermore, the degree of restored blood

flow was indistinguishable from healthy controls in the case-control study. Consistent with the investigators hypothesis, the same patients had no such effect on blood flow while taking the placebo.¹² (See Figure 3)

Limitations included a small sample size of patients and a failure of tadalafil to restore sympatholysis in one BMD patient. Authors recognize that by excluding patients with heart failure, the sample is biased for certain dystrophin mutations and thus without further study, cannot be extrapolated to patients with cardiomyopathy. Finally, as this was a single dose study, it is unsure whether chronic administration will sustain the positive outcome or a tolerance will be developed. Authors state that future studies are being planned to address whether PDE5 inhibitors can slow disease progression and improve muscle strength in a longitudinal multicenter trial.¹²

DISCUSSION

New data in glucocorticoid-treated patients show that chronic treatment does not protect dystrophic muscle from functional ischemia.¹ The need for a disease specific treatment for patients with MD is still unmet. However, promising research has found that PDE5 inhibitors have reduced muscle injury and fatigue in dystrophin deficient mdx mice.⁹ Only a few studies have been done to investigate the impact these drugs have on human patients with MD. The two studies^{4, 12} included in this review both found that functional sympatholysis is impaired in patients with MD and with the use of PDE5 inhibitors such as tadalafil or sildenafil, one can alleviate exercise-induced muscle ischemia. (See Figures 1,2, and 3)

There was little variability across the two studies. The differences that existed for one were with study design. The Nelson et al case-control study⁴ was an open-label design with no blinding of either the patients or the investigators. The study done by Martin et al¹² performed a similar case-control, but was followed up by a randomized double-blind design. Both studies did use a 2-week washout period for crossover to account for tadalafil's longer elimination half-life and although the case-controls were not blinded the outcomes were measured in a straight forward objective manner. Additional differences included the dosing of drugs; whereas Nelson et al⁴ tested 20 and 40 mg each of tadalafil and sildenafil, Martin et al¹² only tested 20 mg of tadalafil alone. Hence the dose dependent effect was only seen in the Nelson et al study.⁴

Other variability between the two studies include the side effects reported. Facial flushing occurred in all the patients receiving PDE5 inhibitors in the Nelson et al study⁴ and two of them experienced penile erections that resolved spontaneously. In contrast, patients in the Martin et al study¹² reported none of these adverse events. Both studies reported no effect on blood pressure. Although the authors did not mention anything further about side effects, a larger and longer studies will clarify whether the benefits outweigh the risks.

The main limitation of these studies is a small sample size of 10 patients each. In the Nelson et al⁴ study all 10 patients had restored sympatholysis in a dose dependent manner when administered either sildenafil or tadalafil. In the Martin et al study,¹² similar result were found in all but one patient. The authors hypothesized that the lack of response in that patient could be due to the type or severity of mutation. Another bias they recognized was by excluding patients with heart failure, the results could not be extrapolated to patients with cardiac involvement.

Despite the small sample size, few variabilities and bias exist across studies suggesting a moderate level quality of evidence based on the GRADE approach. (See Table 1.)

Both studies took into account that being a single dose trial, the question remains as to whether these outcomes can be sustained with chronic administration of PDE5 inhibitors. Patients do not develop tolerance when chronic PDE5 inhibition is used to treat erectile dysfunction or pulmonary hypertension which gives researchers positive hope.¹² Future studies including a larger sample size of subjects over a longer period of time using the optimal dose are still needed to assess whether the drugs can slow disease progression.

CONCLUSION

There is still no disease-specific treatment for patients who suffer from MD. Glucocorticoids may help prolong ambulation for 2 to 3 years, but are intolerable in 25% of patients. Functional sympatholysis, a protective mechanism in muscles of healthy individuals undergoing exercise was found to be impaired in patients with MD. This review found evidence for the use of PDE5 inhibitors in restoring this mechanism thus alleviating exercise-induced muscle ischemia in patients with MD. Whether these results can be sustained with chronic administration remains unknown. Future studies are being planned to answer this question which could lead to determining if PDE5 inhibitors can slow disease progression in patients with MD. If this option is feasible, patients will be able to look forward to a longer life with fewer medical complications including loss of ambulation, cardiac and respiratory difficulties as well as unwanted side effects from glucocorticoid use.

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Table 1. Characteristics of Reviewed Studies

Table I: Quality Assessment of Reviewed Articles								
Study	Design	Downgrade Criteria					Upgrade Criteria	Quality
		Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		
Nelson et al ¹	Case-Control	Not Serious ^a	Not Serious	Not Serious	Serious ^b	Unlikely ^{c,d}	Dose-Response Gradient ^e	Moderate
Martin et al ²	RCT	Not Serious	Not Serious	Not Serious	Serious ^b	Unlikely ^{c,d}	None	Moderate

^a Lack of blinding of data collectors and subjects but strong use of objective measurements
^b Small sample size & few initial studies may overestimate effects
^c Studies were not sponsored by the drug industries
^d Accounted for crossover effect with a 2-week wash out period
^e %TLS increased as the doses increased

Figure 1. Functional sympatholysis is impaired in patients with DMD and rescued by PDE5 inhibitors

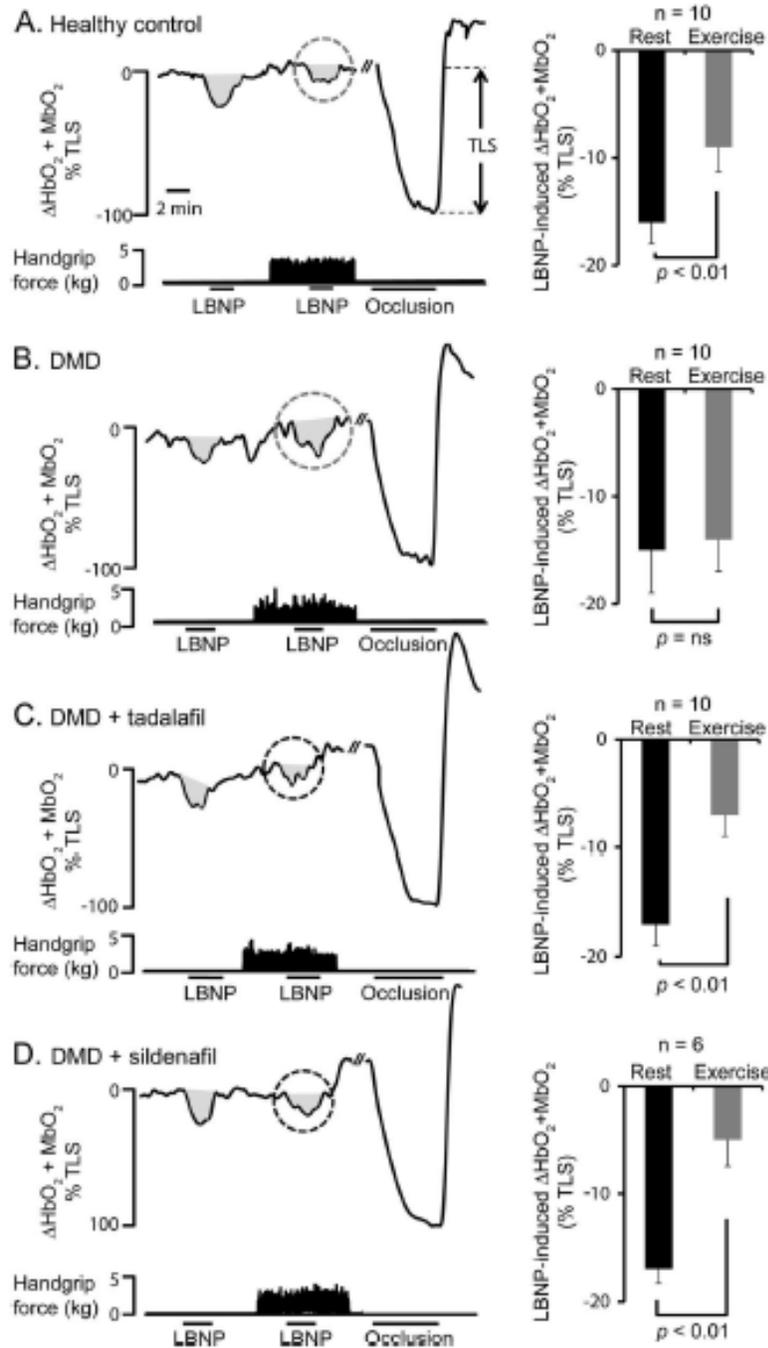


Figure 2. Sildenafil equally restores functional sympatholysis compared with tadalafil. Both drugs do so in a dose dependent manner

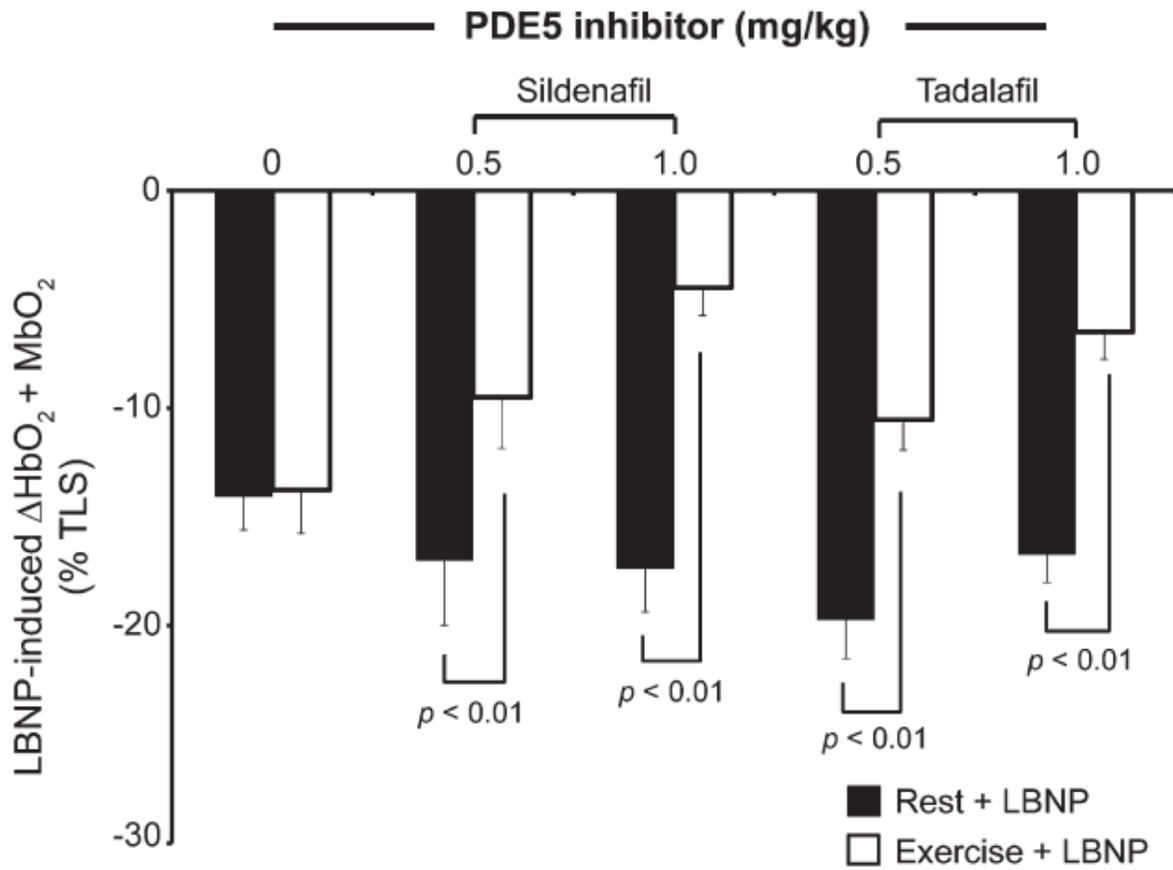


Figure 3. Tadalafil restores functional sympatholysis in contrast to the placebo in patients with BMD

