In new study, common drug reverses common effect of Becker muscular dystrophy

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Cedars-Sinai Heart Institute researchers have found in an initial clinical trial that a drug typically prescribed for erectile dysfunction or pulmonary hypertension restores blood flow to oxygen-starved muscles in patients with a type of muscular dystrophy that affects males, typically starting in childhood or adolescence.

Tadalafil, commonly known by brand names Cialis and Adcirca, reversed the effects of a biochemical chain of events that in Becker muscular dystrophy deprives muscles of an important chemical, nitric oxide, which normally tells blood vessels to relax during exercise, increasing blood flow and oxygenation.

With a single dose, the drug, which works downstream from nitric oxide, fully restored proper blood flow in eight of nine patients in the study, and the effects were "both marked and immediate," according to an article in the journal *Science Translational Medicine*.

"There is no treatment for this progressive muscle-wasting disease and there has been little research. Previous studies in laboratory mice suggested that drugs such as tadalafil could restore proper blood flow, but this is the first study showing that the drug may offer a therapeutic strategy in humans," said Ronald G. Victor, MD, director of the Cedars-Sinai Hypertension Center of Excellence and associate director of the Cedars-Sinai Heart Institute and the Burns and Allen Chair in Cardiology Research. He is the article's senior author.

Becker muscular dystrophy results from a genetic defect that reduces the amount of a protein called dystrophin in the membrane of muscle cells. With insufficient and poorly functioning dystrophin, patients lose muscle strength and have increased risk of heart failure. Affecting 1 in 19, 000 male births, Becker muscular dystrophy is less common and more slowly progressive – but still debilitating—form of Duchenne muscular dystrophy which eliminates all dystrophin, affects 1 in 3,500 male babies born, and usually appears in early childhood.

Victor led the research team that previously discovered the blood flow abnormality from loss of nitric oxide in the muscles of children with Duchenne muscular dystrophy. The new study shows the same blood flow problem is common in adult patients with Becker muscular dystrophy, thereby offering improved blood circulation as a potential avenue for treatment.

The tadalafil study was a double-blind, randomized cross-over trial in which researchers measured forearm muscle oxygenation levels while patients performed handgrip exercise. Patients were evaluated after receiving either a single 20 mg capsule of tadalafil or a placebo. After a two-week break to be sure all drug was out of the patients' systems, the groups were switched. The dose used in this muscular dystrophy study is only one-half the dose approved by the Food and Drug Administration for daily use for adult patients with pulmonary hypertension.

Victor said the blood flow effects in this single-dose trial were dramatic and encouraging but more research is needed before recommending tadalafil for patients with Becker muscular dystrophy.

"Cedars-Sinai is planning longer term studies to determine if correcting muscle blood flow leads to a clinically meaningful outcome," Victor said. "This is not a cure, but it could be the first step toward identifying potential treatments for Becker muscular dystrophy. Providing adequate

oxygenation to muscles already weakened by abnormal dystrophin may be a strategy to slow the course of the disease. Tadalafil already is a well-studied and well-known medication that enjoys a very favorable side-effect profile. This class of drugs has been a major advance even though not a cure for patients with pulmonary hypertension, a serious illness related to insufficient blood flow to the lungs. Since no new drug development would be needed, repurposing it for muscular dystrophy could quickly transform clinical practice."

More information: *Science Translational Medicine*: "Tadalafil alleviates functional muscle ischemia in patients with Becker muscular dystrophy," Nov. 28, 2012.

Provided by Cedars-Sinai Medical Center