Heart drug effective for treating symptom of muscular dystrophy

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A medication most often used to treat heart arrhythmias also reduces a central symptom of myotonic dystrophy, the most common type of muscular dystrophy in adults.

The findings about the medication mexiletine - a chemical cousin of lidocaine - were published May 4 in the journal *Neurology*, a publication of the American Academy of Neurology.

Currently there is no drug approved to treat myotonic dystrophy, an inherited disease that is marked by progressive muscle weakness. While the course of the disease can vary dramatically from patient to patient, symptoms besides weakness can include muscle stiffness, difficulty speaking and swallowing, problems walking, and in some patients, heart problems and cataracts. Physicians estimate that approximately 40,000 Americans have the condition.

The researchers at the University of Rochester Medical Center found that mexiletine is effective at treating the myotonia - muscle stiffness - that is at the center of the disease. Turning a key in a lock, writing with a pen or pencil, picking up and setting down a pitcher of water - all are formidable tasks for patients with myotonia. Sometimes the symptom first occurs when a patient shakes someone's hand, then cannot relax his or her grip for several seconds.

While several doctors have suspected that mexiletene helps relieve myotonia, this is the first placebo-controlled, double-blind study to show

that it actually does so, said neurologist Richard Moxley III, M.D., an author of the study and an international expert on muscular dystrophy.

"It's important for physicians who treat patients to know that mexiletine is an option," said Moxley, who is director of the University's Neuromuscular Disease Center and professor of Neurology. "Several physicians who specialize in treating patients with myotonic dystrophy have found it to be effective for their patients, but we really wanted to study the issue closely. The medication really addresses myotonia quite well, with no additional risk."

The findings come from one of the world's premier groups focusing on research and new treatments for muscular dystrophy. Ten years ago Moxley began the world's first muscular dystrophy registry, which now includes more than 1,500 patients with either myotonic dystrophy or facioscapulohumeral dystrophy.

Moxley also heads the University's Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center, one of three research centers originally created in 2003 by the National Institutes of Health. The Rochester center is now one of six NIH Wellstone centers and most recently received $5 million in additional funding in September 2008 to continue its work for five more years.

In the trial of mexiletine, evaluators measured the amount of time it took patients to relax their grip after squeezing the handles of a computerized device that measures force. For most healthy people, that relaxation takes one-third of a second or less. But for people with myotonic dystrophy, that relaxation can take many seconds.

Scientists studied two groups of 20 patients who had myotonic dystrophy, all confirmed through genetic analysis. Each participant received either placebo, or 150 or 200 milligrams of mexiletine three

times a day, for seven weeks. Then, after a period of several weeks where they received no drug, participants were switched to the other treatment for another seven weeks.

The team found that mexiletine at three daily doses of either 150 or 200 milligrams per dose does a great deal to alleviate myotonia. In their test of relaxation after grip, the team found that mexiletine reduces the abnormally long relaxation by 38 percent at the lower dose and 59 percent at the higher dose. No benefit at all was seen for participants on placebo.

Because the drug can affect the heart, participants in the study were admitted as inpatients and stayed several nights at the University's Clinical Research Center, where their heart health could be monitored closely. The team found no adverse effects of mexiletine, including no effects on normal cardiac rhythms.

Mexiletine acts to help the muscle compensate for the ion channel abnormality that is at the core of the myotonia in this disease. The myotonia is caused by a sort of molecular stutter that causes electrical signaling in muscle cells to go awry, in effect making muscle stick in the "on" position. The mutation markedly reduces the number of functioning muscle chloride channels and causes decreased movement of the chloride ion across the muscle membrane, leading to excessive muscle irritability and repeated spontaneous activation of muscle fibers. This results in muscle stiffness and delayed relaxation after contraction. Mexiletine works through the sodium channel, which is functioning normally, to decrease muscle irritability.

The new research findings on the effectiveness of mexiletine come amid several exciting research finds by Moxley's colleagues. In one line of research, led by Charles Thornton, M.D., researchers have discovered precisely how a faulty gene actually causes myotonic dystrophy by

preventing normal proteins from doing their jobs. Thornton's group then used experimental compounds to break up abnormal cellular deposits of toxic RNA in the nuclei of cells, eliminating myotonia in mice with myotonic dystrophy. Down the hall, a team led by Rabi Tawil, M.D., is part of an international study examining the genetic roots of the second most common form of muscular dystrophy in adults, facioscapulohumeral muscular dystrophy.

Provided by University of Rochester Medical Center