Medical Xpress

Targeted drug therapy prevents exercise-induced arrhythmias

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A 12-year-old Dutch boy - bedridden for three years because of an inherited cardiac arrhythmia syndrome - can now join his friends on the soccer field thanks to a discovery made by Vanderbilt University Medical Center researchers.

The investigators, led by Björn Knollmann, M.D., Ph.D., report this week in Nature Medicine that the clinically available drug flecainide prevents potentially lethal arrhythmias in patients with a specific type of exercise or stress-induced arrhythmia disorder called CPVT.

"It's potentially a breakthrough in the treatment of this rare syndrome," said Knollmann, associate professor of Medicine and Pharmacology.

Patients with CPVT experience abnormally rapid heart rates (tachycardia), usually during exercise or stress, and are at risk for fainting and cardiac arrest. The syndrome kills up to 50 percent of untreated patients, and it may account for some unexplained sudden cardiac deaths in young athletes.

Current treatment has been limited to two medications - beta blockers, often used at very high doses, and calcium channel blockers - to control the arrhythmias.

The Dutch patient, for example, experienced ventricular tachycardia - and ICD shocks - whenever he got out of bed, Knollmann said.

Defibrillator therapy also can be problematic for pediatric patients (CPVT is usually diagnosed in children), who require multiple surgical revisions of their systems.

"For this particular disease, the ICD is a suboptimal treatment," he said. "It's extremely desirable to have a drug treatment that reduces or prevents the ventricular tachycardias, and therefore prevents the ICD shocks."

Knollmann and his team have been studying the molecular defects that trigger arrhythmias. They knew that mutations in two genes that encode calcium-handling proteins, the ryanodine receptor and calsequestrin, cause the disorder.

In 2006, the group discovered how these mutations cause arrhythmias at the cellular level - by allowing calcium to "leak" out of its storage containers inside heart cells. Knollmann's team developed a mouse model for CPVT (by eliminating the calsequestrin gene) and proposed using the model to study medications and interventions for the disorder.

They tried flecainide, a clinically available anti-arrhythmic that is used to treat atrial fibrillation. It worked.

In isolated heart cells, flecainide blocked the ryanodine receptor and the calcium "leak" (the underlying molecular defect in CPVT), and it completely prevented ventricular arrhythmias in the mouse model of CPVT.

"So we knew that this established drug specifically targets the disease mechanism in CPVT," Knollmann said.

With these encouraging results, the investigators teamed with Arthur Wilde, M.D., Ph.D., at the University of Amsterdam, to test flecainide in

two patients with CPVT who continued to have arrhythmias while on conventional therapies - the previously mentioned 12-year-old boy and a 36-year-old woman. The boy has a mutation in the calsequestrin gene, the same gene mutated in the mouse model; the woman has a mutation in the ryanodine receptor, which is more common among CPVT patients.

In both patients, flecainide (combined with a beta blocker in the boy) prevented exercise-induced ventricular arrhythmias. The patients have taken flecainide for more than six months now and are living normal lives.

The group is currently enrolling additional CPVT patients to clearly define the benefits and risks of flecainide and to compare how it works in patients who have varying ryanodine receptor and calsequestrin mutations.

Frank Fish, M.D., a pediatric cardiologist at Vanderbilt, has placed two patients with CPVT on flecainide therapy.

"We're hoping that flecainide is going to allow us to back off the excessively high doses of beta blockers, limit defibrillator discharges in patients with ICDs, and decrease the likelihood that we'll need to implant defibrillators in these patients at a young age if the arrhythmias can be controlled medically," Fish said. "That's an exciting prospect."

Fish feels like he's come full circle with flecainide. In the late 1980s, he surveyed the drug's effects in pediatric patients - as a follow-up to a large clinical trial in adults that showed increased rates of death among heart attack survivors who had ventricular arrhythmias. Fish and his colleagues found an unexpectedly high frequency of pro-arrhythmia among young patients.

"So for 20 years, physicians have been reluctant to use flecainide for

ventricular arrhythmias," Fish said. "It's interesting to now find ourselves turning to a medication we've been fearful of using. In this specific population (CPVT patients), it may turn out to be the magic bullet."

Source: Vanderbilt University Medical Center