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Continuous use of nitroglycerin increases severity of heart attacks, study shows

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When given for hours as a continuous dose, the heart medication nitroglycerin backfires -- increasing the severity of subsequent heart attacks, according to a study of the compound in rats by researchers at the Stanford University School of Medicine.

"Basically it's a cautionary tale," said professor of chemical and systems biology Daria Mochly-Rosen, PhD, senior author of the study that will be published Nov. 2 in *Science Translational Medicine*. "Here is a practice in medicine used for over 100 years. Nitroglycerin is so old that a proper clinical trial has never been formally done. Our study says it's time for cardiologists to examine the value of nitroglycerin treatment that extends for hours at a time."

The study also showed that the damage can be reduced by simultaneous treatment with an enzyme activator known as Alda-1, discovered by Mochly-Rosen and collaborators and reported in Science in 2008.

Nitroglycerin is a mainstay of care for heart disease. It's the go-to medicine for those suffering from bouts of chest pain, known as angina pectoris, who take it as a sublingual tablet or oral spray. And it's a standard treatment for heart attack patients, who get it also through an I.V. drip or patch in the emergency room.

It works like a charm, at least at first, opening vessels so blood can flow to the heart more easily. But sustained use leads to desensitization, a pitfall noticed shortly after the explosive chemical was first used as a

drug, in 1867 -- the same year Alfred Nobel obtained his patents for dynamite, which had nitroglycerin as its main ingredient.

To reduce desensitization to nitroglycerin, modern physicians cycle patients on and off the drug: A typical regimen for hospitalized heart attack patients is 16 hours on, eight hours off. An occasional tablet or spritz is not known to lead to this dampened response.

What wasn't suspected until the last decade was that prolonged use of nitroglycerin could actually harm heart tissue if a heart attack occurs. Among the evidence are observations that nitroglycerin damages cells in the heart by wrecking an important enzyme, ALDH2, which not only mops up toxic products of free radicals, but is the key to nitroglycerin's ability to stave off chest pain. ALDH2 catalyzes the conversion of nitroglycerin to nitric oxide, which reduces chest pain by opening the blood vessels. So by damaging ALDH2, nitroglycerin shoots itself in the foot as a heart disease treatment.

In 2008, Mochly-Rosen and colleagues identified another function of ALDH2: It's a critical enzyme for protecting the heart from damage caused by ischemia, or decreased blood flow -- not just for people being treated with nitroglycerin, but for everyone. So the researchers too became concerned about the safety of sustained nitroglycerin use.

"We knew that nitroglycerin was an important treatment for heart attack symptoms," said Mochly-Rosen, who is also the George D. Smith Professor in Translational Medicine. "And we thought, 'Wait, everyone gets nitroglycerin when they come to the emergency room with chest pains, sometimes in a drip or as a patch. What if they get a heart attack during this period? It could be more severe than if they had not been treated.'"

That led to their current study. Using a rat model, they tested the effect

of sustained nitroglycerin treatment on the severity of heart attacks. They found that nitroglycerin increased heart attack severity in rats. After 16 hours of nitroglycerin treatment, the heart damage was twice as large as in untreated control animals. Five to eight animals made up each group.

Cardiac function was also significantly diminished in relation to the control animals, as determined by echocardiograms immediately after the heart attack and again two weeks later. And when the rats were given the enzyme activator Alda-1 along with nitroglycerin, the detrimental effects of prolonged nitroglycerin treatment were nearly erased.

"We showed unequivocally that the rats were worse off after nitroglycerin treatment, and if we had Alda-1 on board, we protected them," said Mochly-Rosen.

"Nitroglycerin improves blood flow when the vessels are constricting. But what we found is that if you use it for too long, the enzyme that helps protect against tissue damage - ALDH2 - dies. With our animal model, we demonstrated that the loss of this enzyme makes the outcome from the heart attack worse. Nitroglycerin is not benign."

Given the importance of ALDH2 in protecting different tissues, including the heart, nitroglycerin tolerance should not be considered as a simple loss of drug efficacy, said co-author Julio Cesar Batista Ferreira, PhD, a postdoctoral scholar. "Our study was the first to show the nitroglycerin tolerance is associated with increased cardiac vulnerability. Further studies to identify the molecular mechanisms of nitroglycerin tolerance and its side effects are needed."

Alternative treatments to improve blood flow in cardiac patients exist, said cardiologist John Cooke, MD, PhD, a Stanford professor of cardiovascular medicine who was not involved in the study but has

discussed it with the researchers.

"Continuous administration of nitroglycerin by patch or by intravenous infusion, as in the coronary care unit, is initially useful in relieving pain and also favorably influences hemodynamics — reduces blood pressure, improves coronary blood flow. However, extended use of this form of nitroglycerin is known to induce tolerance to its own beneficial actions within 12 to 24 hours," said Cooke, adding that researchers don't yet know the full effects of using the drug for more than 24 hours.

"Professor Mochly-Rosen's work raises additional concern about the extended use of long-acting or continuous administration of nitroglycerin in the coronary care unit," he added. "It is probably best to use nitroglycerin continuously for only short periods of time, and replace the continuous infusion or patch with other medications to reduce symptoms and favorably influence hemodynamics."

In the future, said Mochly-Rosen, nitroglycerin could be made safe by pairing it with Alda-1, if it is proven safe in humans, or another drug with a similar enzyme-activating function.

Provided by Stanford University Medical Center

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