New Drug Developed at UC-San Diego Has Potential to Treat Hypertension and Heart Disease

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Investigators at the University of California, San Diego (UCSD) School of Medicine have developed a new drug called nitrosyl-cobinamide, which they have shown in animal models to be potentially more effective than nitroglycerin in increasing coronary blood flow and lowering blood pressure. The report on this study, led by Gerry R. Boss, M.D., UCSD professor of medicine, is currently on line and will be published in the December 7 issue of *Experimental Biology and Medicine*.

Hypertension and heart disease impact millions of people around the world. Two drugs currently used to treat acute hypertension and angina have negative side effects, making development of new and improved therapies a scientific priority.

"As a vitamin B12 analog, the parent compound of this new drug, cobinamide, appears to be non-toxic at the doses that would be required to treat angina or acute hypertension," said Boss. By coupling cobinamide with nitric oxide (NO), a gas produced by the body's cells that helps regulate a variety of physiological functions including blood pressure and heart function, and which also serves as a neurotransmitter, Boss and his team have developed an effective delivery system for NO to reach its targets and exert its beneficial effects.

Cobinamide, similar in structure to vitamin B12, is a compound resulting during the biosynthesis of vitamin B12 by bacteria. The UCSD investigators have shown that cobinamide binds relatively tightly to nitric oxide (NO) to form nitrosyl-cobinamide. The binding is reversible, so the compound can be used as a "direct" NO donor, meaning it releases nitric oxide without any biological processing required. In contrast, nitroglycerin, which has been used to treat angina for over a century, requires processing by the body, known as biotransformation, for the NO to be released.

Nitroglycerin (and its derivatives), and sodium nitroprusside are two NO donor drugs, which have been in clinical use for many years, each with side effects. Nitroglycerin, made into dynamite by Alfred Nobel in the late 19th century, increases blood flow to the heart by dilating the coronary arteries, and reduces the heart's work load by reducing blood pressure and dilating (opening)

veins. Sodium nitroprusside is used to treat acute hypertensive episodes because of its potent blood pressure lowering properties.

"Unfortunately, neither agent is ideal," said Boss. Nitroglycerin requires biotransformation in the body, and can prove toxic to mitochrondria, the power source to cells. Also, tolerance to nitroglycerin develops rapidly, in large part due to the biotransformation process, causing it to become less effective over time. Drug treatment by nitroprusside is limited because it releases five cyanide ions for every nitric oxide molecule, so it can result in cyanide toxicity in patients.

"A clear need exists for a non-toxic, direct NO donor drug," Boss said, adding that nitrosyl-cobinamide may be such an agent.

Boss and his colleagues showed that nitrosyl-cobinamide was an effective NO donor in several different biological systems: cultured rat pulmonary artery smooth muscle cells, organs of the Drosophila (fruit fly), isolated mouse hearts and aortas, and whole mouse studies. In the isolated mouse hearts and the whole animal studies, the UCSD team showed that nitrosyl-cobinamide was more effective than nitroglycerin in increasing coronary blood flow and lowering blood pressure, respectively.

"The data in our study shows nitrosyl-cobinamide to be a potent and direct releaser of nitric oxide," said Boss, who is seeking to partner with a company to produce nitrosyl-cobinamide once further efficacy testing is complete. Formal toxicology and pre-clinical pharmacokinetic studies are currently underway to determine if the compound causes any side effects.

Additional contributors to the paper include Kate E. Broderick, Luis Alvarez, Mahesh Balasubramanian, Darrell D. Belke, Ayako Makino, Adriano Chan, Virgil L. Woods, Jr., Wolfgang H. Dillmann, Vijay S. Sharma and Renate B. Pilz, UCSD Department of Medicine; and Timothy D. Bigby, UCSD Department of Medicine and VA San Diego Health Care System. The research was funded in part by grants from the National Institutes of Health.

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