Endothelin drugs benefit those with pulmonary hypertension

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Recent research to block the effects of endothelin, a powerful substance that constricts blood vessels and stimulates cell growth, has led to successful treatment of pulmonary arterial hypertension and provides hope for treating other chronic diseases. The usefulness of the new drugs to treat congestive heart failure is much less clear, said Professor Matthias Barton, M.D. of the Department of Medicine at the University of Zurich School of Medicine.

Dr. Barton will give an update on endothelin research at the American Physiological Society's 11th International Conference on Endothelin. The title of his talk is "What You Should Know About Endothelin," is part of the symposium, "Roles of Endothelin-1 on Cardiac Function and Diseases." The conference takes place Sept. 9-12 in Montreal.

What is Endothelin?

Endothelin's importance in both health and disease quickly became clear after researchers first discovered its receptors in the early 1990s, according to Dr. Barton. It is the most potent and longest lasting of the blood vessel constrictors (vasoconstrictors) and is 100 times more powerful than the vasoconstrictor norepinephrine.

The human body continuously produces endothelin and increases its production in response to disease conditions, such as inflammation, high blood pressure or high cholesterol. Nitric oxide, a substance also released

from the endothelium that dilates the blood vessels (vasodilator), helps counterbalance endothelin production.

Endothelin's duties are wide ranging. In addition to being a vasoconstrictor, it also helps regulate cell growth, contributes to heart muscle contractility and helps determine heart rate. That is only a partial list, and it is all beneficial. On the negative side, endothelin can disturb heart rhythm and promote unfavorable changes in the heart muscle following congestive heart failure. Endothelin also promotes kidney disease and coronary artery disease, among other disorders.

Researchers have recently developed drugs in hopes of blocking the negative effects of the most important form of endothelin, endothelin-1. The drugs, including ambrisentan, bosentan, darusentan, enrasentan, sitaxsentan, and tezosentan are endothelin receptor antagonists. That is, they work by preventing endothelin-1 from linking with one or both of its receptors, ETA and ETB. Endothelin cannot work without at least one of these receptors.

Endothelin Receptor Antagonists and Fighting Disease

Clininal trials have begun to use endothelin receptor antagonists to treat pulmonary hypertension, resistant arterial hypertension, proteinuric renal disease, cancer and autoimmune diseases such as scleroderma. The following are some research highlights on endothelin receptor antagonists:

Pulmonary Hypertension. The FDA has approved the use of endothelin blockers to treat human pulmonary hypertension which is a disease with a poor prognosis. The first clinical trials have demonstrated benefits regarding symptoms and have improved the quality of life of the

patients. These drugs targeted either the ETA receptor alone, or both receptors, ETA and ETB, together.

Clinical research so far suggests that endothelin antagonists will be a major part of pulmonary hypertension therapy in the future. Among the issues still to be resolved are whether drugs that block ETA alone will be more effective in treating pulmonary hypertension than drugs that block both ETA and ETB and whether it is best to combine the drugs with other drugs, such as vasodilators.

Proteinuric Renal Disease. Protein excretion in the urine is a reliable predictor of cardiovascular risk. According to the first clinical studies treatment with drugs that block ETA alone, and treatment with drugs that blocks both receptors, reduced protein excretion in the urine in patients with renal failure, even in patients already treated with other anti-proteinuric drugs. Clinical research in this area is ongoing.

Coronary Artery Disease. Research on mice with atherosclerosis (hardening of the arteries from plaque buildup) has found that inhibiting endothelin inhibits the development of atherosclerotic plaque. Also in mice, blocking the ETA receptor alleviates some of the causes leading to angina and can reduce damage to the heart tissue following a heart attack. Finally, chronic treatment with an ETA receptor improves the ability of blood vessels to dilate. This improved vasodilation has also been found in human studies.

Resistant Arterial hypertension. Treatment with a drug that blocks ETA alone, and treatment with a drug that blocks both receptors, substantially reduced arterial blood pressure in human patients with essential or resistant essential hypertension. Further research is necessary to determine whether the drugs can reduce hypertension-related organ damage such as failure of the heart or kidneys or the number of deaths associated with hypertension.

Heart Failure. In several long-term clinical studies with human patients with acute or chronic congestive heart failure, none has shown that the receptor blockers can provide any benefit. Dr. Barton noted that not all of the data from the human trials was available to scientists so that they could further analyze these results. In addition, patients in the trials received the endothelin blockers along with standard treatments for heart failure, perhaps masking the possible benefits of the new drugs, he said. He recommends further research in the area of heart failure, which could possibly include lower drug dosages and close monitoring and treatment of edema in this very ill patient population.

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