News
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***New drug reduces blood cholesterol level.

DALLAS -- An experimental drug called mevinolin has been shown effective in treating people with dangerously high levels of blood cholesterol, according to a group of Dallas researchers.

The mevinolin study was conducted by a team at The University of Texas Health Science Center at Dallas including Dr. Scott Grundy, director of the Center for Human Nutrition; Dr. David Bilheimer, head of the Lipid Metabolism Unit and associate dean for Clinical Affairs at Parkland; Dr. Joseph Goldstein, chairman of the Department of Molecular Genetics, and Dr. Michael Brown, director of the Center for Genetic Disease. Findings were presented by Bilheimer at a recent meeting of the Association of American Physicians in Washington, D.C.

Grundy calls the drug "a significant step forward," comparing mevinolin treatment for high blood cholesterol to insulin treatment for diabetes. "The basic defect in cholesterol metabolism still exists in the patients studied. But treatment with the drug alone or in combination with another drug can bring blood cholesterol levels to about normal."

Two kinds of lipoprotein carry cholesterol in the blood. HDL (high-density lipoprotein), the type that increases with exercise and alcohol consumption, seems to be beneficial. The other type is LDL (low-density lipoprotein). "This is the culprit in atherosclerosis," says Bilheimer. And mevinolin lowers LDL without affecting the level of HDL.

The drug, like the Japanese drug compactin, works by blocking the manufacture of cholesterol within body cells, says Grundy. This forces cells to use the cholesterol in the bloodstream.

"There are several exciting implications from this study," says Bilheimer. "We now have a prototype for very effective reduction of plasma cholesterol. This enables us to ask, 'If we can lower a 300-400 milligram per deciliter (mg/dl) level to 200, can we arrest or reverse atherosclerosis?' We have been unable even to ask the question before."

Six patients with severe forms of an inherited disorder called "familial hypercholesterolemia" (FH) were chosen for the study. All subjects had either suffered a stroke or heart attack or were at increased risk for these problems. All had abnormally high levels of blood cholesterol that were resistant to conventional drug treatment. In some cases, participants were from the same family.

FH, affecting about one in 500 individuals in this country, causes a retention of abnormally large amounts of cholesterol in the blood. Frequently it leads to premature arteriosclerosis (accumulations of cholesterol on artery walls). Left untreated, heart attacks and strokes occur prematurely.

When blood cholesterol becomes excessive, cells in artery walls get force-fed the fatty substance. Bloated cells, described as "foam cells," gradually replace normal tissue. Scar

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tissue eventually forms, hardening and narrowing the vessels with connective tissue and calcium. Blood flow to heart and brain is then reduced with devastating results.

Each patient had the heterozygous form of FH, inheriting a mutant gene from one parent and a normal gene from the other parent. (There is also a rare homozygous form of the disease in which abnormal genes are inherited from both parents. The homozygous form occurs in one out of one million persons and often results in death by the second decade of life.)

The defect in FH, first identified by Goldstein and Brown, is a lack of cell receptors for LDL. These receptors normally draw cholesterol from the blood into cells. Once inside the cell the LDL is degraded, and the cholesterol is freed for cellular use. This process removes LDL from the blood and reduces the threat of arteriosclerosis.

Normal cells produce enough receptors to bind the LDL they need. When cellular cholesterol needs are satisfied, they turn off receptor production. This maintains a constant level of cholesterol within the cell. When cells cannot collect enough circulating cholesterol, they use a back-up capability and produce their own.

If a person lacks receptors, LDL cannot enter cells. These cholesterol-laden molecules are slowly removed from the body by other means, but the delay in their removal allows them to accumulate in the bloodstream and deposit on artery walls.

Patients with heterozygous FH have only about half the normal number of cell receptors; homozygotes have none. The desirable range for blood cholesterol is below 200 to 220 mg/dl. Heterozygous FH patients may have a level of 300-400 while homozygotes may range up to 800 mg/dl.

By blocking the cell's capability to produce cholesterol, mevinolin stimulates the cells in a heterozygous patient to produce more LDL-receptors. It is predicted that the drug would not help the homozygous patient because the cells have no capability of producing the receptors.

When the patient's cells are stimulated to produce more LDL receptors and take cholesterol from the blood, the cholesterol falls to safer levels.

Bilheimer also expects that mevinolin may improve patient compliance. Current therapy has unpleasant side effects and is not always effective in reducing the blood cholesterol to the desired level. Mevinolin appears to be highly effective in reducing the cholesterol level. It was tolerated well by all patients studied, and no toxicity nor abnormalities were noted.

The health science center team plans further studies of patients with FH. However, drugs like mevinolin will not be available to patients who have high cholesterol levels for other reasons until long-term studies for safety have been completed and Food and Drug Administration has been granted.

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