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Anticholesterol drugs risky for some

Long-term threat of cancer could outweigh benefits of medications

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Two physician-researchers who previously questioned the economic and medical wisdom of universal cholesterol testing and treatment are now questioning the long-term safety of the leading cholesterol-lowering drugs.

In an article being published today in *The Journal of the American Medical Association*, Dr. Thomas Newman and Dr. Stephen Hulley of the University of California at San Francisco maintain that two classes of drugs, the fibrates and the statins, could possibly cause cancer.

But an editorial by two other doctors in the journal disputes the thesis.

Fibrates and statins are used by tens of millions of Americans. An estimated four million Canadians have elevated cholesterol and about 500,000 of them regularly take cholesterol-controlling drugs.

At issue is whether a seemingly healthy person with an elevated cholesterol level can expect benefits from long-term use of a cholesterol-lowering medication that would justify any risks associated with the treatment.

The researchers maintain that treatment with the two classes of drugs should be reserved for patients already known to have heart disease or those at very high risk of developing it.

In the past decade, there has been more than a tenfold increase in prescriptions for cholesterol-lowering drugs, mostly for the statins and fibrates. In 1992, the latest year for which U.S. data are available, more than 26 million prescriptions were written for such medications.

Statin drugs prescribed in Canada to lower cholesterol include pravastatin, marketed as Pravachol; simvastatin, sold as Zocor, and lovastatin, sold as Mevacor.

Genfibrozil, a fibrate drug sold in Canada as Lopid, reduces fatty substances in the blood. A warning on the product says that in tests on rats, a dosage 10 times the human dose caused a significant increase in liver cancers and benign liver nodules.

"Cholesterol-lowering drugs are not like most drugs, which are given to people who are sick in hopes of making them well," Dr. Newman said in an interview.

"You can tolerate greater risks in people who are already sick. But cholesterol-lowering drugs are being taken for decades by people who are well, in hopes of keeping them well. For them the projected benefit is smaller and thus the possible risks are more important. Our concern is that the drugs might be associated with an increase in cancer and that this may not be noticed for 20 or more years."

Dr. Hulley said: "We don't want people who should be on cholesterol-lowering drugs to become alarmed by our report. People with a high enough short-term risk of developing coronary disease should not worry about the hypothetical possibility of cancer, which could be decades away."

He listed as high risk anyone who already had coronary disease, and men over 45 and women over 55 with high cholesterol that did not respond adequately to dietary changes, especially people with other factors like smoking, diabetes, obesity or high blood pressure that rendered them at high risk for heart disease.

The evidence for carcinogenicity that the researchers cite is circumstantial, mainly studies showing an increase in cancer in laboratory rodents treated with doses that resulted in blood levels of the drugs that were not much higher than the levels reached in people who took them.

While they concede that there has been no definitive evidence of a cancer risk among people taking the drugs, they point out that the most popular drugs, the statins, have not been used long enough to have caused cancer among users.

Studies of the older fibrates are worrisome, the researchers maintain, because they reveal a small but statistically significant increase in deaths from non-cardiovascular causes, including cancer.

For those who need long-term drug treatment, Dr. Hulley said that two other kinds of cholesterol-lowering drugs, the resin cholestyramine and the vitamin niacin, appear less likely to have long-term adverse effects.

In the accompanying editorial in the journal, two doctors from the University of Arizona College of Medicine in Tucson discounted the possibility of a cancer risk associated with with the fibrates and statins and challenged the evidence on which the concern was based.

Dr. James Dalen, a cardiovascular epidemiologist, and Dr. William Dalton, an oncologist and cancer researcher, said rodents are poor predictors of the ability of a chemical to cause cancer in humans. Although nearly all human carcinogens are also carcinogenic in rodents, the reverse is not true.

The Arizona doctors noted that "approximately 50 per cent of all chemicals tested in rodent bioassays will be identified as carcinogens, a highly implausible proportion."

FURTHERMORE, they said, the doses of the cholesterol-lowering drugs used in the rodent studies are many times greater than what people take and, at such high doses, toxic effects could possibly produce cancer in the animals. In an interview, Dr. Dalton said that at the drug exposure levels reached in human patients, there was no increase in cancer in the laboratory animals.

Countering the editorial comment, Dr. Hulley and Dr. Newman said that most other drugs, including 85 per cent of the drugs used to lower blood pressure, did not cause cancer in rodents.

They argued that it was inappropriate to discount the significance of cancer tests in rodents. They cited the World Health Organization's statement that when data on humans were lacking, it was "prudent" to regard evidence of cancer in experimental animals as indicative of a cancer risk to humans.

Dr. Newman and Dr. Hulley performed no new tests for cancer-causing potential. Rather, they based their warning on rodent studies that had been submitted to the U.S. Food and Drug Administration before the drugs were approved for sale.

The drug agency apparently did not consider the findings cause for keeping the medications off the market, although the agency did limit approval of the fibrate gemfibrozil to certain high-risk patients.

The main hope from the beginning was that these medications would prevent cardiovascular disease, not just delay the inevitable in patients who already had damaged hearts or clogged coronary arteries, Dr. Dalen explained.

Although most studies showed that cholesterol-lowering medications had the greatest benefit for cardiac patients, a study in Scotland published in November showed that the statin drugs could prevent the development of heart disease in healthy middle-aged people with high cholesterol levels.

In the study, pravastatin reduced by 31 per cent risk of heart attack and cardiac death in healthy men aged 45 through 64 who had elevated cholesterol levels. In addition, the overall death rate among the men taking the drug was reduced by 22 per cent and no increase in cancer was seen.

(*continued overleaf*)

Still, Dr. Newman, who is a pediatrician, and Dr. Hulley, an epidemiologist, questioned the wisdom of treating elevated cholesterol levels in young men and women. Dr. Newman also expressed concern that the availability of the statins, which are effective and well-tolerated cholesterol-lowering drugs, had prompted an undue focus on cholesterol levels.

REFERENCE: Newman, T.B. and S.B. Hulley: Carcinogenicity of lipid-lowering drugs. *JAMA* **275**(#1): 55-60 (1996). See also the editorial on pages 67-69 by Dalen, J.E. and W.S. Dalton: Does lowering cholesterol cause cancer? [DC Library call number: PER R15.A48]

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