Do Antihistamines Spur Cancer Growth?

This time of year, millions of people pop antihistamines to stop the sniffling and itching caused by allergic rhinitis, or hay fever. These drugs come in a variety of tablets, capsules, and liquids. Some are available by prescription only; others are packaged in over-the-counter cold, flu, and sinus medications.

Just how safe are these drugs?

A new study suggests that certain antihistamines promote the growth of malignant tumors in mice. At the same time, previous research indicates that some widely prescribed antidepressants demonstrate the same cancer-boosting effects.

"We believe it possible that chronic consumption of many prescription and nonprescription drugs with tumor-growth-promoting properties may represent a previously unrecognized, and therefore insidious, environmental risk factor for cancer growth," says Lorne J. Brandes of the University of Manitoba in Winnipeg, chief author of the new report.

Brandes and his Canadian colleagues describe their findings in the May 18 JOURNAL OF THE NATIONAL CANCER INSTITUTE.

In February, a team led by the Department of Health and Human Services' Devra Lee Davis documented a disturbing rise in U.S. cancer incidence even after factoring in the aging of the population (SN: 2/12/94, p.102).

Could modern society's propensity to reach for a prescription panacea explain that deadly increase in cancer? Brandes thinks so. Others warn that caution about the findings is in order.

"We need more information," says epidemiologist Douglas L. Weed of the National Cancer Institute in Bethesda, Md. It's very difficult to draw conclusions about the human impact of such drugs from rodent studies, he adds.

The Canadian research began with the knowledge that a compound called DPPE — a chemical cousin of the anticancer drug tamoxifen — binds to specific molecules called histamine receptors inside the cell. Once bound to those receptors, DPPE spurs malignant cells to divide more rapidly.

Brandes and his colleagues wondered if other chemicals, similar to DPPE, would do the same thing. In a paper published in the July 1, 1992 CANCER RESEARCH, his team demonstrated that antidepressants such as amitriptyline (Elavil) and fluoxetine (Prozac) stimulated malignant growth in rodents at doses equivalent to those taken by humans.

Now, the Canadian team has done the same type of experiment with five common antihistamines: loratadine (Claritin), astemizole (Hismanal), hydroxyzine (Atarax), doxylamine (Unisom and Nyquil), and cetirizine (Reactine).

Why test antihistamines? This class of drug resembles DPPE and binds to the same intracellular histamine receptors. The Canadian team began to entertain the alarming possibility that such antihistamines also could prod existing cancer cells to grow more aggressively.

To test that theory, the researchers first injected mice with a solution of cancer cells, either melanoma (a type of skin cancer) or fibrosarcoma (a connective tissue malignancy). Then, mice in the treatment group received one of the five antihistamines at daily doses equivalent to what humans take for the average case of the sniffles. Mice in the control group got daily shots of a harmless solution. After 18 to 21 days of such treatment, the researchers removed the tumors and compared the weights of the tumors from each group.

They report that three of the five antihistamines appeared to speed up the growth of the cancer injected into mice. Loratadine and astemizole significantly boosted the growth of both melanoma and fibrosarcoma, and hydroxyzine promoted the development of just melanoma.

In contrast, doxylamine and cetirizine appeared to do nothing to the tumors in these rodents.

Some drug manufacturers disagree with those findings. A press statement released by Janssen Pharmaceutica, the maker of astemizole, calls the new research "preliminary." Schering-Plough Corp., which markets loratadine, says the company's own research shows no evidence that the drug promotes malignant tumor growth.

By all accounts, the drugs in question do not cause cancer. But the new study suggests that they may rev up the proliferation of a cell that's already malignant.

Here's how, the researchers speculate. These antihistamines diffuse through a cell's membrane. The drugs then bind to the histamine receptors and thus interfere with the so-called P-450 enzyme system, a group of enzymes that helps detoxify poisons and aids in regulating cell growth.

If the cell is otherwise healthy, that disruption may not do much. But if the cell has already been hit by a cancer initiator, the alterations in the P-450 system may tip the cell over the edge. That cell now begins to divide in the out-of-control fashion characteristic of cancer.

Brandes and his colleagues believe that some antihistamines follow a bell-shaped curve in promoting cancer: They don't necessarily spur growth at very tiny or extremely high doses. Indeed, coauthor Frank S. LaBella, also at the University of Manitoba, says his research indicates that there's an optimal range at which a malignant cell gets the message to grow.

LaBella speculates that at low to moderate doses of antihistamines the perturbation in the P-450 system tells the malignant cell to proliferate. But at very high doses, that system shuts down; in some cases, the cell may even die.

Fluoxetine and amitriptyline may work the same way to spur the development of cancer, LaBella and Brandes say. However, a study by Raymond A. Bendele and his colleagues at Eli Lilly & Company's toxicology laboratory in Greenfield, Ind., found no evidence that fluoxetine boosted the growth of rodent tumors. Eli Lilly markets fluoxetine.

Yet when Brandes' team took the published Eli Lilly data and reanalyzed it, they found a familiar bell-shaped curve. That as-yet-unpublished reanalysis shows that rats who received moderate doses of fluoxetine appear significantly more likely than controls to develop lung tumors.

The debate has potentially serious public health implications. Brandes points out that many people suffering from cancer become clinically depressed and are treated with antidepressants.

His team is calling on the U.S. Food and Drug Administration and Health Canada to put warning labels on fluoxetine, amitriptyline, and the three antihistamines that caused tumor promotion in mice. In addition, the researchers want the regulatory agencies to revamp the current drug screening process, which doesn't look for tumor promotion at clinically relevant doses.

Canadian and U.S. officials say they have no plans to take such action, at least for now. FDA's Gregory Burke says the agency wants to replicate the Canadian team's findings. They're also considering launching an epidemiological study to see whether such drugs are linked to cancer in humans.

"There's a need to validate these findings," concurs Health Canada's Brian Gillespie. Both Burke and Gillespie say they will continue to monitor the scientific evidence on these drugs. "There are a number of questions that need to be addressed," Gillespie adds.

— K.A. Fackelmann