

A Death During Research

Apparent Supplement Overdose Killed Healthy Volunteer

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A healthy 70-year-old nurse who volunteered for an Alzheimer's disease study at Case Western Reserve University died in May from complications of an apparent overdose of a common dietary supplement administered during the research.

Elaine Holden-Able became confused and severely ill on April 4, suffering a cardiac and respiratory arrest a few hours after a hospital dietary aide gave her a dose of methionine, a normal constituent of animal protein that is also sold as a supplement. She was resuscitated but remained hospitalized in an intensive care unit at University Hospitals of Cleveland, a Case Western Reserve affiliate. She died on May 6.

The levels of methionine measured in Holden-Able's bloodstream four hours after she received the dose were the highest that have ever been recorded -- and about 10 times higher than would have been expected had she received the proper dose, said S. Harvey Mudd, a methionine researcher at the National Institute of Mental Health who participated in a review of the case.

"We can't prove that she got an overdose, but I can't think of any other explanation," he said yesterday.

Holden-Able's death predated that of Ellen Roche, a healthy volunteer who died in June after participating in a Johns Hopkins asthma study. However, unlike the review of the Roche case, which led the federal Office of Human Research Protection (OHRP) to suspend most of Hopkins's federally funded medical research, an OHRP review of Holden-Able's death has essentially absolved Case Western Reserve and University Hospitals.

Although OHRP officials apparently knew of her death while investigating the Hopkins case last summer, university and hospital officials did not publicly announce that a volunteer had died in the Cleveland study until December. In the preceding month, OHRP informed officials at the two institutions that it had found "no evidence to substantiate" concerns that researchers had failed to minimize the risks to participants. Holden-Able's death was first reported in December by the Cleveland Plain Dealer.

"OHRP knew about it. Nobody was told anything," said Vera Hassner Sharav, president of the Alliance for Human Research Protection. "Now they're saying, 'Oh, but everything is fine.' The major issues are left out."

The study, which researchers immediately halted after Holden-Able became ill, was designed to examine how healthy people metabolize methionine, an amino acid that is an essential part of the diet. In the body, methionine is converted into homocysteine. Studies suggest that people with high blood levels of homocysteine are at increased risk for heart disease, hardening of the arteries and, perhaps, Alzheimer's.

Mudd said study participants were supposed to receive a "loading dose" of methionine, calculated according to the recipient's weight. In Holden-Able's case, it should have been 8.3 grams. He said thousands of people have received such doses without serious side effects as part of research studies and diagnostic tests. About 20 percent of recipients experience some dizziness, confusion or nausea.

On April 4, a nurse in the hospital's clinical research unit gave a dietary aide a verbal order to weigh out 8,300 milligrams of methionine, mix it in orange juice and give it to Holden-Able, said Eric Cottington, associate vice president for research of Case Western Reserve University. The order was not written down, and the aide may have made a mistake while converting the dose from milligrams to grams, he said.

When the bottle used for Holden-Able's dose was examined later, about 96 grams was missing. The aide told investigators that she had given Holden-Able the proper dose. She told them that later, when Holden-Able became ill, she had weighed out additional doses of 8.3 grams and 83 grams and had visually compared them to check herself.

Two hours after taking the dose, Holden-Able began vomiting and became extremely confused and agitated, Cottington said. Transferred to the emergency room, she had trouble breathing and suffered a cardiac arrest. She subsequently developed adult respiratory distress syndrome, a severe lung disorder, and died several weeks later.

Except for high blood pressure, Holden-Able was in "perfect health," said John Scharon, a lawyer retained by her nieces and nephews. He said no lawsuit has been filed. The study, led by University Hospitals' Robert Friedland, had one other participant, who suffered no ill effects.

Mudd said some schizophrenics, as well as a few healthy volunteers, were given up to 20 grams of methionine daily for five days in studies done during the 1960s and 1970s to see whether the dietary component was involved in exacerbating the symptoms of the mental illness. He said that a significant percentage of recipients developed dementia, delusions and disorientation, and that they got better after they were taken off the supplement.

He said Holden-Able's symptoms "sound similar, in more extreme form," to the effects seen in the schizophrenics.

In its review, the OHRP concluded that the researchers had reported Holden-Able's illness and death properly and had taken adequate steps to minimize the risks to the study participants. OHRP plans no further action in the case, said William Hall, a spokesman for the Department of Health and Human Services.

An internal review by the hospital ethics board recommended that only licensed dietitians should weigh and administer dietary supplement doses, Cottington said. In the future, only hospital pharmacists will be allowed to prepare such doses, he said.

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