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Miracle cure that kills claims fifth victim

Experimental hepatitis B drug trial goes fatally wrong after doctors miss early clue

BY LAURAN NEERGAARD
Associated Press

A fifth volunteer died in the United States yesterday from an experimental drug touted as a miracle cure for hepatitis B. The patient was beyond medical rescue even as scientists unravelled the mystery of what went gravely wrong in a clinical trial.

The first clue was in plain sight a year ago, but researchers at the National Institutes of Health did not know enough about the drug to recognize what it meant, the study's lead scientist said.

"Something terrible happened and we missed it," Dr. Jay Hoofnagle said in an emotional interview describing the horror of realizing the drug was killing people months after they stopped taking it.

"The dreadful thing [is] waiting to see what will happen," he said, his voice trembling, before learning of the latest death. "I just hope we're over the worst."

The drug Fialuridine (FIAU) had shown great promise for fighting the hepatitis B virus, which can cause deadly cirrhosis and liver cancer. When dogs passed toxicity tests unharmed, the Food and Drug Administration approved FIAU for human trials.

Too late, scientists would discover that in humans, FIAU stealthily attacks the very building blocks of cells in livers, kidneys and nerves.

Five people treated with FIAU have died of liver and kidney failure, despite liver transplants for three of the patients. Yesterday, a 37-year-old woman died after two months in critical condition and two liver transplants at the University of Virginia Medical Center. One volunteer remains in serious condition there.

Another is recovering from an Aug. transplant at Emory University Hospital in Atlanta.

Dr. Hoofnagle now fears that other anti-viral drugs such as the AIDS drugs AZT and ddI – known to be toxic – may attack patients as FIAU does.

The first clue that FIAU was dangerous appeared in August of last year when a man who had taken FIAU developed painful nerve damage. Paul Melstrom of Pheonix and 23 other volunteers participated in a 28-day NIH study of FIAU, from mid-April to mid-May. Almost four months later, Mr. Melstrom, 53, contracted severe neuropathy in his feet and legs. Another patient had minor neuropathy.

"It was so obvious to me it was the FIAU," Mr. Melstorm said from Arizona. "There's nothing about my life that changed in 1992, but there was one hallmark event. That was the taking of the FIAU."

But the NIH could not prove that FIAU was to blame. Many factors cause neuropathy, including alcohol. Mr. Melstrom is a recovering alcoholic and once had a bout with mild neuropathy.

So the agency continued the trial this spring, giving the drug to 15 otherwise healthy hepatitis patients for up to 11 weeks. Dr. Hoofnagle did warn volunteers beforehand that neuropathy was a possible side-effect and tested them for symptoms.

In early June, two volunteers developed neuropathy symptoms and immediately stopped taking FIAU. By mid-month, they were hospitalized with liver poisoning, unrelated to their hepatitis but similar to the late toxicity Mr. Melstrom had experienced.

Dr. Hoofnagle halted the trial, but the horror was just beginning.

One by one, from June 16 through August, seven people fell ill with damaged livers, kidneys and nerves, as frustrated doctors and frightened fellow volunteers looked on.

Now, with five of the seven dead, the remaining eight patients in the trial are being watched to determine whether they escaped serious harm.

What happened? This is Dr. Hoofnagle's theory:

A virus cannot reproduce on its own, so it instead takes over a cell's DNA, the cellular blueprint that maps how each person's unique genes are continuously reproduced. The virus uses the DNA to replicate itself furiously.

In the trials, FIAU foiled the hepatitis B virus by forming a bogus link in a hepatitis-infected DNA chain that stopped it from reproducing.

FIAU did not stop there, however. It also tricked sub-units of the body's cells called mitochondria, which have their own DNA that FIAU also crippled. This crippled DNA produced a second generation of flawed mitochondria that killed the cells dependent on them for energy.

Stopping the drug at that point did not halt the problem because the genetic damage had already been done.

Mr. Melstrom exhibited that damage sooner than the other patients because the mitochondria of nerve cells reproduce faster than those of liver cells, Dr. Hoofnagle said. Doctors did not realize, however, that his neuropathy signalled worse disease to come.

"In retrospect, [the connection] seems obvious," Dr. Hoofnagle said. "But we followed on course because we hoped FIAU would make their hepatitis get better. We weren't looking for toxicity any more."

The NIH now knows that FIAU did not poison the test dogs because dogs have a natural enzyme that renders the drug inactive, Dr. Hoofnagle said.

Government scientists will meet on Sept. 21 in Washington to review Dr. Hoofnagle's data, including his concern that similar antiviral drugs could also be dangerous.

"This toxicity is not in FIAU alone," Dr. Hoofnagle said. "This toxicity ..... probably has been seen for many years and not recognized."

At least one expert on antiviral drugs is skeptical.

Dr. Raymond Schinazi of Emory University found in 1986 that FIAU under certain conditions would metabolize into a very toxic compound. He thinks the NIH volunteers fell victim to that still-unexplored metabolite of FIAU, rather than to damaged mitochondria.

And, he says, AIDS drugs don't attack mitochondria.

"They're very different," Dr. Schinazi said. "AZT doesn't kill people the way FIAU does."

But Dr. Hoofnagle thinks scientists will be amazed by what they don't know about mitochondria.

"It was considered a minor issue," he said. "This is going to change all that."

The article EM9330 reprinted above is used in Figure 2.1b of the STAT 220 Course Materials, in Figure 3.1 of the STAT 231 Course Materials and in Statistical Highlight #22.