



Unanticipated Risk in Clinical Research

Principles and Practice of Clinical Research

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Unanticipated injuries to research subjects erode public trust in research and lead to progressive changes in research regulation, oversight, and conduct



An Unexpected Death in a Gene Therapy Trial: Background

- Investigators at U of P and their partners in industry invent an adenovirus vector that expresses ornithine transcarbamylase
- Approval granted by IRB, IBC, RAC, FDA to conduct clinical trials in OTC-deficient patients
- Research patient Jessie Gelsinger dies



An Unexpected Death in a Gene Therapy Trial: Reactions

- NIH, FDA, DHHS, Congressional investigations and hearings
- Prolific media coverage
- New mandates for DSMB, AER, clinical research training and conflict of interest reporting
- Creation of OHRP; IRB closures
- Lawsuits
- Withdrawal of investigator privileges



Questions Asked on 'The Morning After'

- Protocol: Scientifically and ethically appropriate?
- Patient consent: Fully informative?
- Investigator training: Adequate?
- Financial conflicts: None?
- Approvals: All obtained and updated?
- Subject selection: Appropriate?



Questions Asked on 'The Morning After'

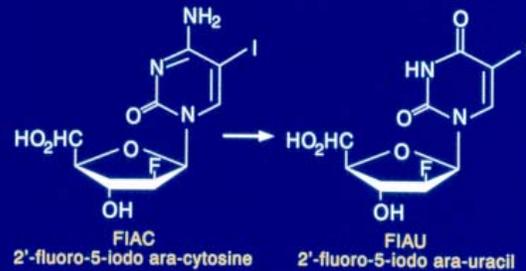
- Protocol adherence: Consistent?
- SAEs: Identified? Reported promptly?
- Documentation: Complete?
- Study monitoring: Independent?
- Data entry: Accurate?
- Statistical analysis: Valid?
- Reports: Objective?

A Failed and Dangerous Approach to Viral Hepatitis

1970's

- Synthesis at Sloan-Kettering of fluoropyrimidine analogues FIAU and FIAU
- At the time, a search was on for selective inhibitors of virus replication

FIAU Metabolism



Antiviral Activity of FIAU

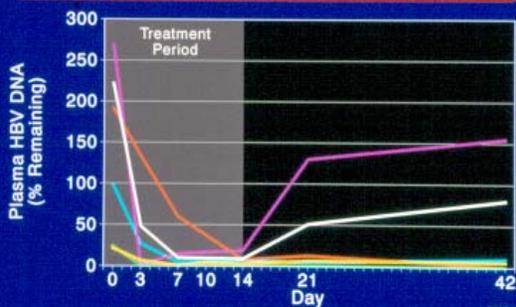
	ED ₉₀ (μ M)	ID ₅₀ (μ M)
HSV-1	0.05	-
HSV-2	0.10	-
VZV	0.01	-
CMV	2.50	-
HBV DNA polymerase	-	0.05*

*vs 0.90 for ACV

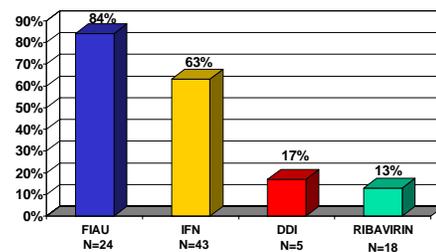
Early Testing of FIAU and FIAU

- 1983 Phase I-II studies of IV and oral FIAU for 5-10d in cancer and AIDS patients. Not effective for CMV and causes nausea, fatigue
- 1990-91 Oral FIAU at 1 mg/kg for 14d markedly suppresses HBV levels in HIV patients, with 'acceptable' side effects

Effect of FIAU on HBV DNA



Nucleoside Analogs vs Interferon Inhibition of HBV DNA Levels



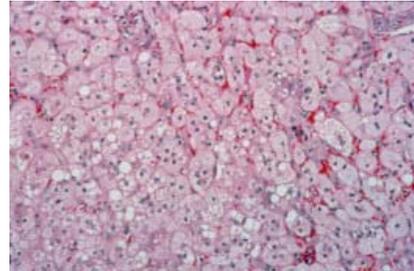
A Death After a Longer Course

1992

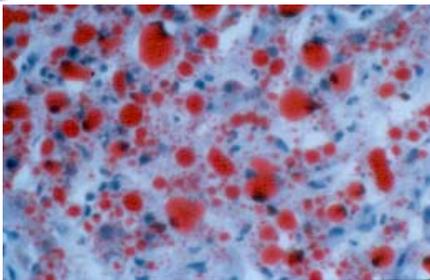
NIH trial in 24 HIV-negative HBV pts: FIAU 0.05-0.5 mg/kg/d x 28d. Dose-related inhibition of HBV DNA. ALT 'flares.'

Complications: peripheral neuropathy and cholecystitis 4 mo after FIAU; neuropathy and hepatic failure 3 mo after treatment - dies 2 mo later. Autopsy - microvesicular fat!

Microvesicular Changes in an FIAU-Treated Patient



Lipid-Filled Vesicles in an FIAU-Treated Patient



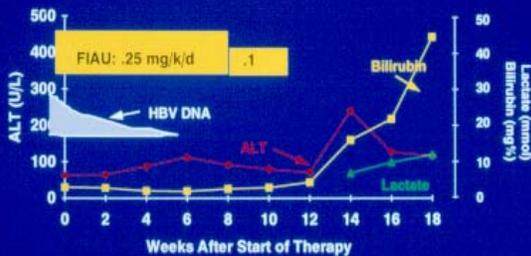
Multi-Center Trials Begin and End

- March 1993 Eli Lilly multi-center trial of 0.1 vs 0.25 mg/kg/d x 90d. NIH 180d trial: 15 pts enrolled

- May-June 1993 Dose reduced or stopped for GI upset in 3 pts and tingling in one. One pt admitted for fatigue and nausea.

- June 26, 1993 Patient presents with lactic acidosis. Trial is stopped.

FIAU IN CHRONIC HEPATITIS B Patient No. 1



Crisis in the Study Group

- July-August 1993 Despite termination of FIAU, 5 pts die of progressive liver failure, lactic acidosis, pancreatitis, myopathy and neuropathy. Two survive with emergency liver transplantation. Five suffer reversible effects. Three remained well.
- The investigations begin**

FIAU in the Media

- Newspapers, magazines, radio, and TV report patient deaths
- Trial design and consent forms criticized
- Investigators accused of negligence for ignoring clues to FIAU's dangers
- Summary reports on the sequential investigations

And Then the Patients Suddenly Started Dying

How NIH Missed Warning Signs in Drug Test
NASH POST, 9-7-93

By John Schwartz
 Weekly #1 • 10th Edition

For months, Jay Hoofnagle and his staff at the National Institutes of Health had been discounting the complaints of some of their patients. Several had told the doctors that the experimental drug they were taking for chronic hepatitis B was causing side effects, from nausea and weight loss to a painful tingling in the feet.

The doctors had conducted extra tests, but found nothing unusual. They told the patients that their symptoms were not threatening and probably were not caused by the drug, fialuridine (FIAU). After all, FIAU had seemed relatively safe and wonderfully effective for some patients in two previous tests.

Then the patients started to die. On June 25, Howard Tschener, a 44-year-old Arlington man, checked into an emergency room with failure of his liver and other organs. He



NIH spokeswoman
 ... toxicity of drug was 'unlike others'

"He sneezed, and said, 'Susan, I'm not going to die.'" Hoofnagle reached Lee by telephone, and told him to get back to Bethesda right away.

Lee died on July 30, poisoned by FIAU. The drug cleared Lee's body of the hepatitis virus, but it destroyed his liver, pancreas and other major organs in the process. Of the 15 patients in the NIH trial, 10 had taken FIAU for more than a month. Eventually seven of those had to be sent to transplant centers for new livers. Five, including Lee, have since died; one is still hospitalized in fair condition following a liver transplant.

Optimism May Have Led to Drug Tragedy

By John Schwartz
 Washington Post Staff Writer

Optimism may have led scientists to evaluate information in too favorable a light and miss warning signs about an experimental drug that killed at least five people, the Food and Drug Administration said yesterday.

The FDA's own rules about reporting and reviewing new drug data contributed to the tragedy involving the drug fialuridine (FIAU), the report said. The task force recommended broad reforms of FDA drug testing regulations that would require scientists to gather more data about adverse effects and make researchers assume from the outset that medical problems in patients in the studies were caused by the drug, agency officials said.

"The Food and Drug Administration has adopted its findings," said FDA Commissioner David A. Kessler, and "we're beginning work now" to draft new regulations.

The drug was touted as a promising treatment for chronic hepatitis B, a disease affecting about 300

million people in the United States. The report said that optimism about the drug led researchers and the drug's corporate sponsors to evaluate patient problems in the most favorable light. Problems that might have been caused by FIAU were routinely attributed to other drugs the patients had been taking, to other medical conditions the patients had or to hepatitis itself. Also, many problems were missed because FIAU's toxic effects are delayed, showing up after the drug trials.

The panel examined previous human trials of FIAU and a closely related drug, FIAU, conducted by Orlasen Pharmaceuticals Inc. in the late 1980s and early 1990s. The task force looked for abnormally high levels of liver enzymes in patients in those studies, a sign of hepatic inflammation.

In the earlier FIAU tests, researchers commonly attributed the high enzyme levels to "flaring," a sign that the patient's body was

A fourth "re-dosed" patient from that study suffered a severe attack of pancreatitis and recovered. Another patient died following a 1992 test of the drug. By 1992, Orlasen had licensed the drug to Eli Lilly & Co.

The FDA task force stressed that not every one of the side effects and deaths could be blamed on the drug, but said that the accumulation of similar cases would have served as a warning warranting further study. NIH officials would not comment on the report.

A Lilly spokesman said "this tragedy was completely unpredictable and unexpected."

The panel's recommendations would require researchers and sponsors of new drugs to report regularly all incidents of adverse events, deaths and patients dropping out of studies for safety reasons. Sponsors of new drugs would be required to perform a "worst-case" analysis of the data, assuming

NIH Responses

- 1993-1994 NIH Director's Advisory Committee reviews all records and interviews patients and investigators. Concludes that the studies were appropriate, conducted according to "the best of current clinical practice," and that the FIAU toxicity is "a novel type of reaction that was unexpected."

FDA Investigations

- Aug, 1993 All records inspected
- Nov, 1993 Inspection reports cite lack of prompt notification of deaths
- May, 1994 FDA 'Warning Letters' conclude inadequate consent forms, and poor clinical judgment
- Oct, 1994 FDA proposes new regulations for documenting and reporting SAEs

Congress Weighs In

- Oct, 1993 The House Committee on Government Operations raises "serious questions of possible misconduct." Requests an 'impartial' DHHS review of the study.
- June 1994 The House DH Committee calls the NIH Director's investigation a "whitewash." Demands an independent review by the IOM.

Institute of Medicine Review

- June 1994** Commissioned by the Secretary, DHHS. All records reviewed again, and all investigators, patients, sponsors, and FDA Medical Officers are interviewed.
- March 1995** The IOM concludes that the studies were justified, properly designed, and well conducted. There was "no evidence of negligence." The proposed FDA reporting guidelines are considered to be excessive.

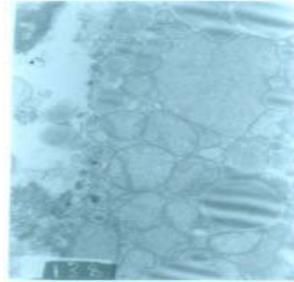
Legal Issues

- Aug, 1993** Private and NIH legal counsel sought by the investigators
- Nov, 1993** First lawsuit filed. Referred to the Department of Justice for defense under the Federal Tort Claims Act
- 1994** Additional suits filed
- Dec, 1995** All lawsuits are settled out of court

The Scientific Community Responds

- Public interest groups decry 'lack' of clinical research safeguards
- Industry points out inherent risks of clinical research
- Ethicists debate informed consent and the competing loyalties of clinical investigators
- Hepatitis drug development ceases for 2 years
- Meetings on treatment and mechanisms

Dilated, 'Empty' Mitochondria



Mechanisms of FIAU Toxicity

- Utilized by gamma polymerase and incorporated into nuclear and mitochondrial DNA
- Loss of mitochondrial oxidative function
- Microvesicular fat accumulation
- Lactic acidosis
- Liver failure, pancreatitis, myopathy, neuropathy

The Host for the Woodchuck Hepatitis Virus





Recommendations Emerging from FIAU Episode

- Preclinical studies: Study in relevant animal models. Still may not predict all events in humans.
- Training: For all PI's and associate investigators
- Review: Separate scientific and ethical reviews with relevant expertise. Support IRB's and train their members.



Recommendations (cont.)

- Consent forms: Uniform consent text; Simplify and shorten; emphasize dialogue; update; document electronically
- Follow up: Adequate for the nature and known risks of trial materials
- Data entry: Create one set of electronic records for all study patients. Support data management



Recommendations (cont.)

- Reporting: 'harmonize' all reporting forms and requirements.
- Monitoring: Formalize and support DSMB's. Provide on-line access to study records.
- Incentives: Reward clinical research conduct and participation. Cover study-related injuries.



Conclusion

Efforts to eliminate risks to those who participate in (and conduct) clinical research have made the process ever harder, without (as yet) enhancing public trust



National Institute of Allergy and Infectious Diseases
National Center for Complementary and
Alternative Medicine
National Institutes of Health

U.S. Department of Health and Human Services