

HEPATIC FAILURE AND LACTIC ACIDOSIS DUE TO FIALURIDINE (FIAU), AN INVESTIGATIONAL NUCLEOSIDE ANALOGUE FOR CHRONIC HEPATITIS B

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Abstract Background. We describe severe and unexpected multisystem toxicity that occurred during a study of the antiviral nucleoside analogue fialuridine (1-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)-5-iodouracil, or FIAU) as therapy for chronic hepatitis B virus infection.

Methods. Fifteen patients with chronic hepatitis B were randomly assigned to receive fialuridine at a dose of either 0.10 or 0.25 mg per kilogram of body weight per day for 24 weeks and were monitored every 1 to 2 weeks by means of a physical examination, blood tests, and testing for hepatitis B virus markers.

Results. During the 13th week lactic acidosis and liver failure suddenly developed in one patient. The study was terminated on an emergency basis, and all treatment with fialuridine was discontinued. Seven patients were found to have severe hepatotoxicity, with progressive lactic acidosis, worsening jaundice, and deteriorating hepat-

ic synthetic function despite the discontinuation of fialuridine. Three other patients had mild hepatotoxicity. Several patients also had pancreatitis, neuropathy, or myopathy. Of the seven patients with severe hepatotoxicity, five died and two survived after liver transplantation. Histologic analysis of liver tissue revealed marked accumulation of microvesicular and macrovesicular fat, with minimal necrosis of hepatocytes or architectural changes. Electron microscopy showed abnormal mitochondria and the accumulation of fat in hepatocytes.

Conclusions. In patients with chronic hepatitis B, treatment with fialuridine induced a severe toxic reaction characterized by hepatic failure, lactic acidosis, pancreatitis, neuropathy, and myopathy. This toxic reaction was probably caused by widespread mitochondrial damage and may occur infrequently with other nucleoside analogues. (N Engl J Med 1995;333:1099-105.)

WORLDWIDE, chronic infection with the hepatitis B virus (HBV) is a major cause of morbidity and mortality from liver disease, cirrhosis, and hepatocellular carcinoma.¹ In the United States, approximately 1 million people have chronic hepatitis B, the complications of which account for 5 to 10 percent of cases of cirrhosis and liver transplantation.

There is no completely satisfactory therapy for chronic hepatitis B. Interferon alfa is now approved for use in this disease, but a four-to-six-month course produces long-term remissions in only one third of patients.²⁻⁵ Furthermore, interferon must be given parenterally, is often poorly tolerated, and is expensive. Clearly, better antiviral therapies are needed.

Among antiviral agents, the nucleoside analogues have been most widely evaluated as potential therapies for chronic hepatitis B. Adenine arabinoside (vidarabine)⁶ and its monophosphate,⁷ acyclovir,⁸ didanosine,⁹ zidovudine,¹⁰ and ribavirin¹¹ have been studied in chronic hepatitis B, but all were either ineffective or too toxic for prolonged use. Recent *in vitro* and *in vivo* models of HBV infection^{12,13} have permitted the identification of several new, orally bioavailable antiviral agents with marked inhibitory activity against HBV. These second-generation nucleoside analogues include 3'-thiacytidine (lamivudine),¹⁴ famciclovir,¹⁵ and fialuridine (1-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)-5-iodouracil, or FIAU).^{16,17}

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In two preliminary dose-finding studies, two- and four-week courses of fialuridine led to prompt and marked suppression of serum HBV DNA levels by 65 to 95 percent.^{18,19} However, there was sustained loss of viral DNA in only a few patients. The possibility that longer courses would be more efficacious led to a trial of a six-month course of fialuridine, an investigational drug. This study was begun in March 1993 but was terminated on an emergency basis 13 weeks later when hepatic failure and lactic acidosis suddenly occurred in one of the patients. In this report, we describe the clinical features of this toxicity, which, despite immediate discontinuation of the medication, eventually led to hepatic failure, lactic acidosis, and pancreatitis in seven patients, of whom five died. Two others survived after emergency liver transplantation.

METHODS

This phase 2 trial was designed to evaluate the safety and efficacy of a six-month course of fialuridine in 24 patients with chronic hepatitis B. Patients were randomly assigned to receive either 0.10 or 0.25 mg of fialuridine per kilogram of body weight per day given orally in two or three divided doses. Fialuridine was provided as a liquid formulation by Oclassen Pharmaceuticals (San Rafael, Calif.) and administered under an Investigational New Drug Application held by Eli Lilly and Company (Indianapolis) for use in chronic hepatitis B.

Entry criteria included the presence of chronic hepatitis B without hepatic decompensation or other serious medical illnesses. All patients had histologic evidence of chronic hepatitis B on the basis of liver biopsy (performed within one year of entry), persistent elevations in serum aminotransferase activities, and the presence of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and HBV DNA in serum for at least six months. Exclusion criteria included serologic evidence of hepatitis C, hepatitis D, or human immunodeficiency virus (HIV) infection.

While receiving therapy, the patients were seen in the outpatient clinic every one to two weeks, were questioned regarding symptoms and side effects, and underwent a physical examination and a battery of blood and urine tests. The blood tests included measurements of serum alanine and aspartate aminotransferases, creatine kinase, alkaline phosphatase, bilirubin, albumin, blood urea nitrogen, and creatinine; a complete blood count; and assays for HBV markers. Radio-

immunoassays (Abbott Laboratories, North Chicago, Ill.) were used to test for HBsAg, HBeAg, anti-HBs, and anti-HBe, and liquid-phase hybridization was used to test for HBV DNA (Genostics, Abbott) (limit of detection, approximately 2 pg per milliliter).²⁰

Details of the protocol were approved by the institutional review board of the National Institute of Diabetes and Digestive and Kidney Diseases, and all patients gave written informed consent.

RESULTS

Characteristics of the Patients

Between March 24 and June 16, 1993, we enrolled 15 patients (13 men and 2 women) in the trial, ranging in age from 29 to 64 years (mean, 44). Twelve were white, two Asian, and one black. The source of hepatitis was believed to be sexual contact in seven, occupational exposure in three, and familial exposure in two and was unknown in three. The patients had had documented chronic hepatitis B for 1.1 to 11.7 years (mean, 5.2). Eleven had participated in a study involving a 4-week course of fialuridine and had completed therapy 7 to 13 months earlier. Eight patients had previously received recombinant interferon alfa, and six had received other nucleoside analogues without sustained beneficial responses.

Aminotransferase Levels and HBV Markers

Levels of HBV DNA decreased in all patients during therapy, the average decline by week 4 being 92 percent in the group given 0.10 mg of fialuridine per kilogram per day and 93 percent in the group given 0.25 mg of fialuridine per kilogram per day. Among the 10 patients who were treated for at least eight weeks, HBV DNA became undetectable in 6 during therapy (Fig. 1). In one patient (Patient 9), HBeAg became undetectable and anti-HBe developed, along with a decrease in serum aminotransferase levels into the normal range. In the other patients, alanine aminotransferase levels were relatively unchanged and HBsAg and HBeAg remained detectable.

Early Side Effects

During the first eight weeks of treatment there were few side effects. One patient had intermittent crampy abdominal pain; another had paresthesias in the feet. Thereafter, increasing fatigue developed in six patients, nausea in five, numbness and tingling in the feet or hands in four, crampy lower abdominal pain in three, constipation in two, and mild thrombocytopenia in one. These clinical changes led to a reduction in the dose in four patients between weeks 10 and 11 and discontinuation of the drug in three between weeks 10 and 12. Thirteen weeks into the trial, Patient 2, in whom fialuridine therapy had been stopped 17 days earlier because of paresthesias, was admitted to a local community hospital because of the sudden onset of hepatic failure, shock, and lactic acidosis (Fig. 2). The study was terminated immediately. All patients were contacted and told to stop taking fialuridine and to return for evaluation.

Severe Fialuridine-Induced Toxicity

Hepatic Failure and Lactic Acidosis

Follow-up evaluations of the patients in the days after treatment was stopped revealed that seven (including Patient 2) had varying degrees of hepatic failure

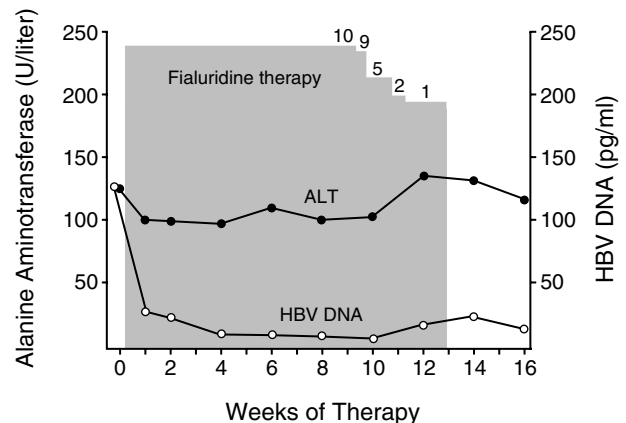


Figure 1. Mean Serum Levels of HBV DNA and Alanine Aminotransferase (ALT) in 10 Patients Who Were Treated with Fialuridine for at Least Eight Weeks.

Fialuridine was stopped after 9 to 13 weeks of therapy; the numbers above the shaded area indicate the numbers of patients still receiving treatment. Values for weeks 14 and 16 were obtained from seven and five patients, respectively.

and lactic acidosis (Table 1). All seven had received fialuridine for at least nine weeks, with cumulative doses ranging from 551 to 1753 mg. Most of the seven patients had fatigue, nausea, constipation, and abdominal pain. All seven had steadily worsening jaundice (Fig. 3A), decreasing hepatic synthetic function, gradually worsening prothrombin times (Fig. 3B), and increasing serum ammonia and lactate levels (Fig. 4). Frank acidosis with hyperpnea and increased anion gaps became evident after lactate levels exceeded 12 mmol per liter.

All seven patients were treated with intravenous infusions of thymidine (8 g per kilogram per day) in an attempt to reverse the effects of fialuridine, which is a thymidine-based nucleoside analogue,²¹ and with oral uridine (24 g per day) to replenish intracellular pyrimidine stores.²² Neither thymidine nor uridine produced obvious clinical improvement. The patients also received intravenous glucose. In several instances serum lactate levels decreased with daily infusions of 2 to 3 liters of 20 percent glucose.

The hepatic failure and lactic acidosis were rapidly progressive in Patients 2 and 7, who were transferred to liver-transplantation centers within four days of admission. After initial treatment with a hepatic-assist device²³ did not reverse the hepatic failure, these two patients underwent emergency liver transplantation.²⁴ The condition of both was hemodynamically unstable at the time of transplantation, and the patients died 22 and 36 hours later with relentless lactic acidosis, profound hypotension, and little evidence of graft function.

Five patients (Patients 1, 3, 4, 6, and 10) had a more gradual progression of hepatic failure and lactic acidosis (Fig. 3 and 4). Their condition deteriorated over a period of several weeks, and they were transferred to transplantation centers 10 to 29 days after admission and 13 to 48 days after fialuridine was stopped. In all five, hepatic decompensation and profound lactic acidosis ultimately developed. Two patients (Patients 1 and 4) died of hemodynamic collapse due to pancreatitis and lactic acidosis before liver transplantation could be

performed, and a third (Patient 6) died of complications of pancreatitis after transplantation. Transplantation was successful in the remaining two patients, resulting in a prompt reversal of the lactic acidosis as well as other signs of hepatic failure.²⁴ They were discharged from the hospital 16 and 94 days after transplantation. During 24 months of follow-up, they have had no evidence of residual fialuridine-induced toxicity except for a mild peripheral neuropathy. Both have been treated with high doses of hepatitis B immune globulin, and neither has had evidence of recurrence of hepatitis B.

Pancreatitis

All seven patients with severe hepatotoxicity had biochemical evidence of pancreatitis, with progressive increases in serum lipase levels (up to a 50-fold increase). Concomitantly measured serum amylase levels remained normal except in three patients who had severe abdominal pain and clinically apparent pancreatitis, which ultimately contributed to their deaths. All five patients who died had both gross and microscopic evidence of pancreatitis at autopsy.

Neuropathy and Myopathy

Five patients with severe hepatotoxicity had symptoms or signs of peripheral-nerve injury. These consist-

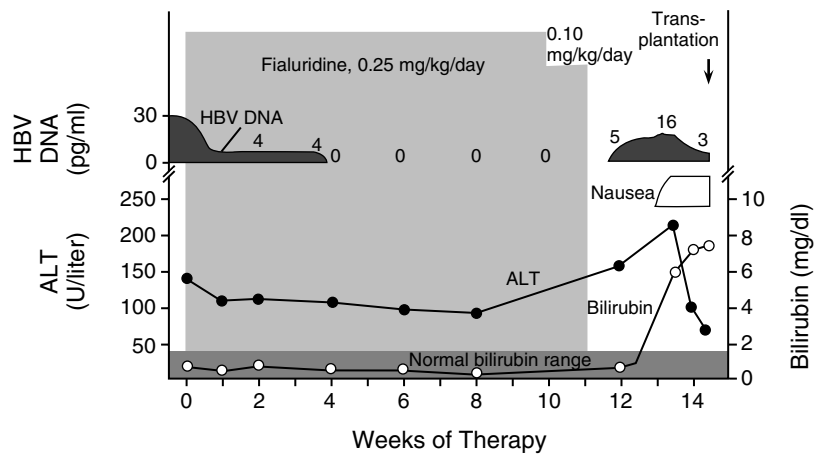


Figure 2. Clinical Course of Patient 2, in Whom Hepatic Failure and Severe Lactic Acidosis Developed after Treatment with Fialuridine for Chronic Hepatitis B.

The dose of fialuridine was decreased at week 10, and treatment was discontinued at week 11 because of paresthesias. Two weeks after therapy was stopped, nausea, vomiting, and weakness developed and the patient was hospitalized with jaundice, lactic acidosis, and shock. He died two days after orthotopic liver transplantation with hemodynamic collapse unresponsive to high doses of inotropic agents. ALT denotes alanine aminotransferase. To convert values for bilirubin to micromoles per liter, multiply by 17.1.

ed of paresthesias and dysesthesias in the feet or toes that were mild to moderate in severity. Clinical findings were subtle, consisting of mild reductions in vibratory sensation and responses to light touch and decreased ankle reflexes. Two patients reported muscle pain or weakness. Muscle and nerve biopsies were performed in two patients with severe hepatotoxicity (Patients 3 and 10). Histologic analysis of muscle showed rare ragged-red fibers, occasional subsarcolemmal cracks, and in-

Table 1. Characteristics of the Patients at Base Line and at the Termination of the Study.*

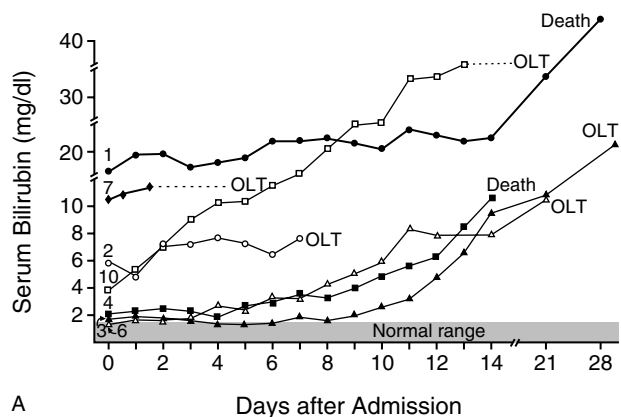
PATIENT NO.	BASE-LINE FEATURES		FEATURES AT TERMINATION OF STUDY										OUTCOME
	HISTOLOGIC FINDINGS	PREVIOUS DOSE OF FIAU	INTERVAL BETWEEN FIAU TREATMENTS	DOSE OF FIAU	DURATION OF TREATMENT	TOTAL DOSE OF FIAU	DEGREE OF TOXICITY	BILIRUBIN	PROTHROMBIN TIME	ALBUMIN	AMMONIA	LACTATE	
		mg	wk	mg/kg/day	wk	mg		mg/dl	sec	g/dl	μmol/liter	mmol/liter	
1	CAH	247	47	0.25	11	1366	Severe	16.0	13.8	3.1	44	6.9	Died
2	CAH	476	41	0.25	11	1218	Severe	5.8	15.4	2.8	77	18.8	Transplantation, died
3	CAH, BHF	121	39	0.10	13	678	Severe	1.6	15.0	3.9	45	3.3	Transplantation, alive
4	Cirrhosis	134	37	0.10	10.5	628	Severe	1.7	14.4	3.4	71	2.2	Died
5	CAH	663	41	0.10	11.5	743	Mild	0.8	11.3	4.4	22	1.6	Alive
6	CAH	115	35	0.10	10.5	551	Severe	4.3	15.1	2.8	48	6.4	Transplantation, died
7	CAH	1353	32	0.25	11	1753	Severe	10.5	15.1	2.6	57	8.3	Transplantation, died
8	CAH	89	43	0.10	10	420	Mild	0.8	12.5	3.7	30	1.9	Alive
9	CAH	1050	36	0.25	10	1216	Mild	0.8	11.5	4.5	24	1.8	Alive
10	CAH, BHF	154	38	0.25	9.5	1716	Severe	3.9	13.2	3.5	11	2.9	Transplantation, alive
11	CAH	0	—	0.10	3	185	None	0.7	11.0	4.2	19	1.9	Alive
12	Cirrhosis	0	—	0.10	3	156	None	0.9	11.4	4.0	42	1.1	Alive
13	CPH	0	—	0.25	1.5	176	None	0.8	10.9	4.4	19	2.4	Alive
14	CAH	0	—	0.25	1.5	193	None	0.5	10.8	4.0	38	0.8	Alive
15	CAH	210	54	0.10	1.5	66	None	0.5	11.9	4.1	21	1.6	Alive
Normal values								<1.2	<13.7	>3.8	<35	<2.2	

*FIAU denotes fialuridine, CAH chronic active hepatitis, BHF bridging hepatic fibrosis, and CPH chronic persistent hepatitis. To convert values for bilirubin to micromoles per liter, multiply by 17.1. Downloaded from www.nejm.org on November 28, 2009. For personal use only. No other uses without permission. Copyright © 1995 Massachusetts Medical Society. All rights reserved.

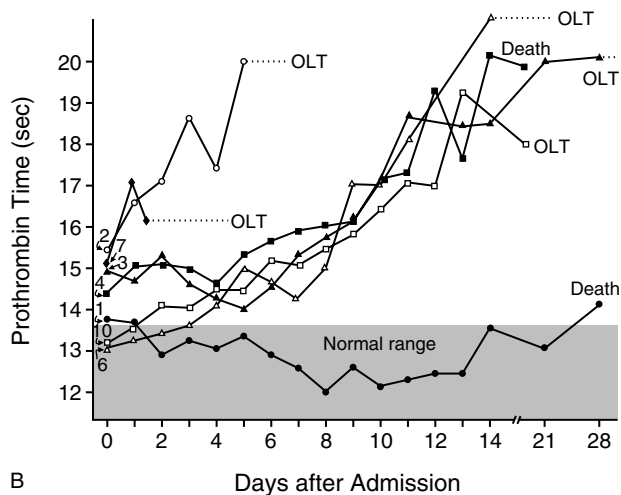
creased amounts of lipid. These changes are similar to, but milder than, those observed with zidovudine-induced myopathy.²⁵ Nerve biopsies revealed a mild focal loss of myelin and mild interstitial fibrosis.

Mild Fialuridine-Induced Toxicity

Mild hepatotoxicity occurred in three patients (Patients 5, 8, and 9) who had received fialuridine for 10 to 11.5 weeks and had received cumulative doses of 420 to 1216 mg, which were comparable to the cumulative doses in the seven patients with severe hepatotoxicity (Table 1). These patients had nausea and abdominal discomfort along with increasing aminotransferase elevations and slight decreases in serum albumin and fibrinogen. These abnormalities were mild, developed two to three weeks after fialuridine was stopped, and generally resolved within 4 to 12 weeks. Patient 5 had mild epigastric discomfort and slight increases in serum



A



B

Figure 3. Results of Serial Determinations of Serum Bilirubin (Panel A) and Prothrombin Time (Panel B) in Seven Patients with Severe Hepatotoxicity Due to Fialuridine.

Values are plotted for each patient (identified by the number given in Table 1) beginning the day of admission after the discontinuation of fialuridine. The outcome for each patient — orthotopic liver transplantation (OLT) or death — is shown at the approximate time of occurrence. Dotted lines indicate the absence of values or times when the values were obscured by interventions (hepatic-assist device or plasma exchange). To convert values for bilirubin to micromoles per liter, multiply by 17.1.

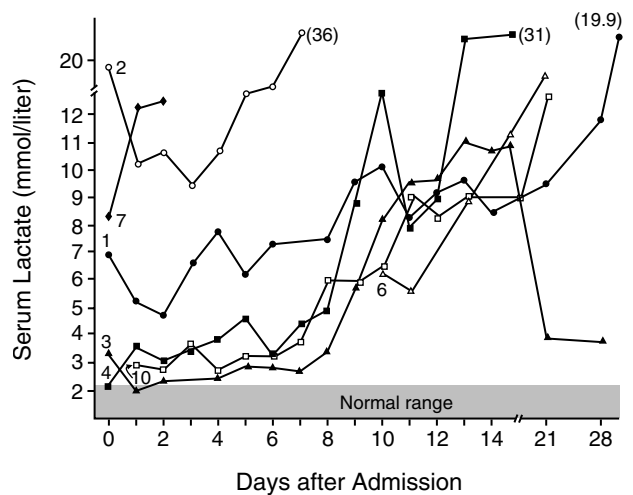


Figure 4. Results of Serial Measurements of Serum Lactate in Seven Patients with Severe Hepatotoxicity Due to Fialuridine. Values are plotted for each patient (identified by the number given in Table 1) beginning the day of admission after the discontinuation of fialuridine. Final values for some patients are given in parentheses.

amylase and lipase levels that persisted for eight months but ultimately resolved completely. In Patient 9 HBV DNA and HBeAg became undetectable during treatment; the other two patients remained positive for HBV DNA, HBeAg, and HBsAg.

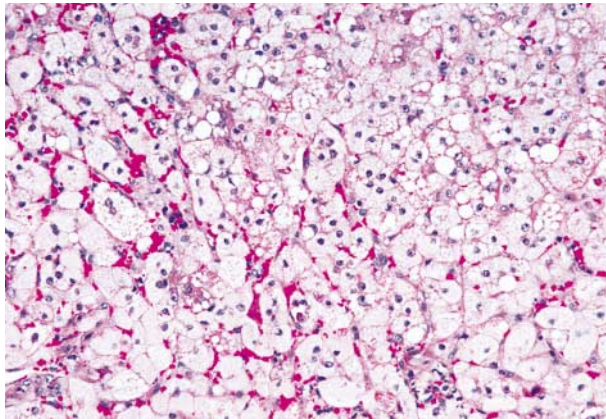
Absence of Fialuridine-Induced Toxicity

Five patients (Patients 11, 12, 13, 14, and 15) received fialuridine for less than four weeks (Table 1), with total doses of less than 200 mg. None had obvious clinical or biochemical evidence of fialuridine-induced toxicity. Serum aminotransferase levels remained unchanged and serum bilirubin, albumin, and lactate levels were normal on multiple occasions. During 24 months of follow-up, these five patients have had no evidence of fialuridine-induced toxicity.

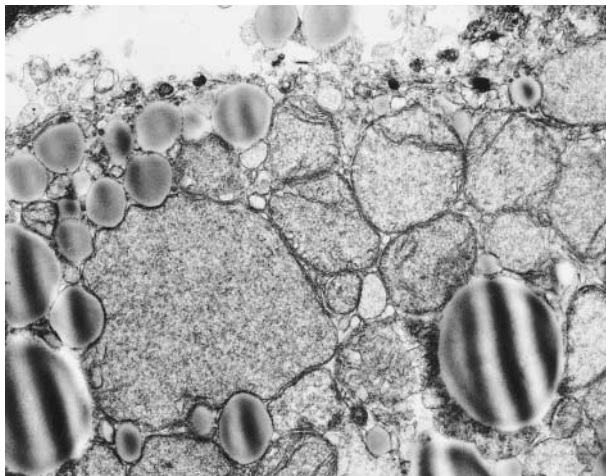
Histologic Evidence of Fialuridine-Induced Hepatotoxicity

Liver tissue was available from the explants of the five patients who underwent transplantation and was obtained at autopsy from the two patients who died without transplantation. Histologic analysis revealed moderate to marked microvesicular and macrovesicular steatosis and cholestasis (Fig. 5A). The degree of inflammation and hepatocellular necrosis was largely unchanged from that present in liver-biopsy specimens obtained before treatment. Electron microscopy documented abnormalities of mitochondria and the accumulation of small droplets of fat (Fig. 5B). All seven patients with severe hepatotoxicity had evidence of chronic hepatitis, and three had cirrhosis. Immunoperoxidase staining for hepatitis B core antigen was positive in six of the seven patients.

Percutaneous liver biopsies were done within two to six weeks of the discontinuation of fialuridine in all three patients with mild hepatotoxicity and in two of the five patients with no evidence of hepatotoxicity. As compared with the histologic findings before treatment,



A



B

Figure 5. Photomicrographs of Liver-Tissue Explant from Patient 2, Who Received Fialuridine (0.25 mg per Kilogram per Day) for 11 Weeks.

Lactic acidosis and hepatic failure developed 17 days after fialuridine was stopped, and the patient required emergency liver transplantation 1 week later. In Panel A histologic examination under light microscopy revealed pale and swollen hepatocytes with marked accumulation of microvesicular fat (hematoxylin and eosin, $\times 450$). The hepatic architecture was preserved, and there was only focal and mild necrosis of hepatocytes and mild cholestasis. The degree of necrosis and inflammation was similar to that present before fialuridine therapy.

In Panel B, electron microscopy of the cytoplasm of a single hepatocyte shows swollen, misshapen mitochondria that have decreased numbers of cristae ($\times 19,000$). Non-membrane-bound fat droplets of various sizes are present.

there was a mild-to-moderate increase in microvesicular and macrovesicular steatosis in Patients 5 and 8 but no appreciable change in the degree of steatosis, necrosis, or inflammation in the other three patients (Patients 9, 11, and 12).

DISCUSSION

In this phase 2 study of the antiviral agent fialuridine, a severe and progressive form of hepatic failure and lactic acidosis developed in 7 of the 15 study patients. This severe toxic reaction was seen after 9 to 13 weeks of therapy and with cumulative doses of only 551 to 1753 mg of fialuridine. Five patients died of re-

lentless lactic acidosis with or without hemorrhagic pancreatitis. Two patients survived after successful emergency liver transplantation. The syndrome of fialuridine-induced toxicity did not resemble typical fulminant hepatic failure in that serum aminotransferase levels were minimally elevated, bilirubin increases were initially slight, and lactic acidosis was severe and relentless. Instead, the fialuridine-induced toxic reaction resembled the fulminant hepatic steatosis that occurs with Reye's syndrome, acute fatty liver of pregnancy, and toxic reactions produced by high-dose tetracycline and valproic acid.²⁶

The severe toxicity of fialuridine was not predicted by preclinical studies in laboratory animals, which had shown no evidence of hepatic, pancreatic, skeletal-muscle, or nerve damage. Furthermore, pilot studies of fialuridine given for two to four weeks to 43 patients with HIV infection¹⁸ and 24 patients with chronic hepatitis B¹⁹ had not revealed obvious hepatotoxicity on initial analysis. However, the underlying chronic hepatitis B and HIV infection may have obscured fialuridine-induced hepatotoxicity. Among the 67 patients treated in the pilot studies, 3 died of liver disease and 1 of pancreatitis within six months of completing therapy. Extensive reevaluation of these pilot studies by an expert committee of the Institute of Medicine concluded that some of these events may have represented delayed toxic effects of fialuridine.²⁷ Indeed, three months after a one-month course of fialuridine and several weeks after a cholecystectomy, intractable ascites followed by lactic acidosis developed in one patient. Autopsy revealed microvesicular fat in the liver, which — in retrospect — makes it likely that fialuridine-induced toxicity played a part in the worsening hepatic function. The other patients who died within six months of receiving fialuridine in the pilot studies were infected with HIV; two died of end-stage liver disease attributed to the progression of viral hepatitis, and one died of pancreatitis attributed to didanosine therapy; none had microvesicular fat in the liver on autopsy.

The onset of the severe hepatotoxicity in the present study was sudden. In most instances, the results of liver-biochemistry tests remained unchanged from pretreatment values in the one to two weeks before the onset of hepatic failure. Most patients with severe hepatotoxicity, however, had a one-to-two-week prodromal period of increasing fatigue, nausea, and crampy abdominal pain. Despite the discontinuation of therapy, the lactic acidosis, hepatic failure, and pancreatitis worsened relentlessly.

Several features of the multisystem toxicity suggested that it was related, at least in part, to widespread, severe mitochondrial injury. First, the clinical picture of hepatic failure resembled that of Reye's syndrome in its progression of symptoms and in the early appearance of hepatic synthetic dysfunction, hyperammonemia, and lactic acidosis, despite minimal increases in aminotransferase levels and mild jaundice.²⁶ Second, the toxicity predominantly affected organs and tissues that have a slow turnover of cells and a major dependence on mitochondrial function. Finally, light microscopy of liver specimens showed marked accumulation of

microvesicular fat, with scant hepatocellular necrosis. Electron microscopy revealed abnormal mitochondria and confirmed the presence of microvesicular fat.

In vitro studies suggest that some toxic reactions induced by the nucleoside analogues may be caused by mitochondrial injury.²⁸⁻³² Zidovudine, didanosine, and zalcitabine inhibit the DNA polymerase γ of mitochondria. Serving as chain terminators, these drugs block the elongation of the mitochondrial DNA chain and deplete mitochondrial DNA to varying degrees. In contrast, recent short-term in vitro studies indicate that fialuridine has minimal effects on the amount of mitochondrial DNA³³ but becomes efficiently incorporated into cellular and mitochondrial DNA and causes increased lactate production by cells.³⁴⁻³⁶ Fialuridine differs from most other antiviral nucleoside analogues in having a hydroxyl group and thus being unblocked at the 3' position of the deoxyribose molecule, which permits its incorporation into nascent DNA chains. Thus, the cellular injury caused by fialuridine may be due to the synthesis of defective mitochondrial DNA, leading to reduced amounts of mitochondrial DNA or to abnormal enzymes encoded by mitochondrial genes.

Clinically, the multisystem toxicity of fialuridine resembles that of several of the other nucleoside analogues. For instance, zidovudine has been associated with a toxic myopathy characterized by the depletion of mitochondrial DNA in myocytes.³² More recently, treatment with zidovudine has been linked to "idiopathic" lactic acidosis and cases of severe fatty liver and hepatic failure.³⁷⁻⁴⁰ A similar syndrome of hepatic failure and fatty liver has been reported after treatment with didanosine^{41,42} and zalcitabine.³⁷ Finally, pancreatitis as a toxic consequence of didanosine treatment is well known, and "chemical" pancreatitis occurs in as many as 50 percent of patients treated with didanosine for prolonged periods.⁴³

Thus, the multisystem toxicity associated with fialuridine in our patients resembled the recognized but uncommon toxic reactions produced by other nucleoside analogues. This suggests that the toxicity of this class of compounds might be related to generalized mitochondrial injury, with individual agents having a propensity to injure particular target tissues: muscle in the case of zidovudine, peripheral nerves in the case of zalcitabine, pancreas in the case of didanosine, and liver in the case of fialuridine. The greater toxicity of fialuridine may relate to its chemical structure, which permits its incorporation into DNA. Confirmation of this hypothesis and further elucidation of the drug's toxicity may have important implications for patients treated with antiviral nucleoside analogues.

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