Articles

Isoniazid-Related Fatal Hepatitis

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To describe the clinical and demographic characteristics of fatal hepatitis due to single-drug isoniazid preventive therapy for tuberculosis, we did a survey of cases from state health departments, published case reports, and reports to the Centers for Disease Control and Prevention from 1970 to 1992. Of 108 reported cases, some clinical information was available for 76. A medical review panel judged 39 of these deaths as probably due to isoniazid hepatitis and 23 deaths as possibly due to isoniazid hepatitis. Of the 62 probable and possible cases combined, 50 (81%) were female, 49 (79%) were non–Hispanic black or Hispanic, and 19 (31%) were younger than 35 years. The median duration of isoniazid preventive therapy before symptom onset was 16 weeks. Of the 60 cases with symptom information, 54 (90%) presented with jaundice. Of the 62 cases, 26 (42%) were monitored monthly in accordance with current recommendations, and 6 of the patients were younger than 35 years. We estimate that the rate of fatal isoniazid hepatitis among patients in the public sector was no greater than 4.2 per 100,000 persons beginning therapy and no greater than 7 per 100,000 persons completing therapy. Adherence to isoniazid preventive therapy guidelines apparently reduces, but does not eliminate, the risk of fatal hepatitis. Careful patient selection, education, and monitoring are critical for minimizing that risk.

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Since its introduction in 1952, isoniazid has been widely used as a single agent to prevent active tuberculosis in persons infected with *Mycobacterium tuberculosis*. It is currently the only agent approved by the US Food and Drug Administration (FDA) for that purpose. Early clinical trials demonstrated the effectiveness of isoniazid preventive therapy and failed to show clinically important toxicity.[1-3] Case series[4-6] and cohort studies[7-9] subsequently revealed, however, that administering isoniazid can rarely result in serious hepatotoxicity and death.

The Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, and the American Thoracic Society have recommended isoniazid preventive therapy, with interim modifications of the indications for its use, since 1965.[10-17] Isoniazid preventive therapy plays a large role both in the 1989 strategic plan to eliminate tuberculosis and the 1992 action plan to combat multidrug-resistant tuberculosis.[18-19] The increase in tuberculosis incidence rates since 1985 in the United States has prompted a renewed emphasis on tuberculin skin test screening and isoniazid preventive therapy.[20] In addition, isoniazid is effective in preventing tuberculosis in persons infected with the human immunodeficiency virus (HIV).[21] Reports of fatal isoniazid-associated hepatitis[22-24] have reignited debate about the widespread use of isoniazid preventive therapy.[25-27]

A recent search of available databases found 177 possible cases of fatal isoniazid hepatitis in the United States between 1965 and 1989.[28] The study lacked clinical information about the suspected cases, however, and the authors could not be certain that all had indeed taken isoniazid preventive therapy. Although published reports of specific cases typically include clinical information, they lack a uniform case definition, and they usually do not reflect a systematic case-finding effort.[29] In one report, the rate of fatal isoniazid hepatitis was estimated to be 14 per 100,000 persons who started isoniazid therapy.[28] In another the rate of fatal isoniazid hepatitis was estimated to be 1 per 100,000.[29] The limitations of these data result in considerable uncertainty concerning the magnitude of fatal liver toxicity from isoniazid preventive therapy.

As part of a CDC-sponsored study of risk factors for fatal hepatitis from isoniazid preventive therapy, we attempted to obtain clinical data for all suspected cases in the United States from 1970 to 1992 for subsequent review by an expert panel. We describe the cases and indicate where possible whether the CDC guidelines for isoniazid preventive therapy were followed.

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ABBREVIATIONS USED IN TEXT

AST = aspartate aminotransferase
CDC = Centers for Disease Control and Prevention
FDA = US Food and Drug Administration
HBsAg = hepatitis B surface antigen
HIV = human immunodeficiency virus
IQR = interquartile range

Patients and Methods

Potentially eligible cases were those who reportedly died in the United States of isoniazid-related hepatitis from 1970 to 1992 after receiving preventive therapy with isoniazid as the single antituberculous agent. In our search for cases, we pursued all those reported in the medical literature, and we contacted all state health departments and those of selected large metropolitan areas. When state health departments lacked a centralized reporting mechanism for suspected cases, we also contacted local health departments in areas that reported a substantial number of active tuberculosis cases. In addition, the CDC Division of Tuberculosis Elimination provided a list of suspected cases that had come to their attention. Although other data sources (such as the FDA Adverse Reaction Reporting System and the National Center for Health Statistics multiple-cause death tapes) include reports of possible cases,[28] patient identifiers that could lead to medical records are not available from these sources.

We collected all available clinical information for suspected cases: health department records, hospital records, histology reports and liver tissue sections, postmortem examination results, and death certificates. A medical panel reviewed all records and tissue sections for suspected cases; the panel comprised an infectious disease specialist, a gastroenterologist specializing in hepatology, and a pathologist skilled in liver diseases. The medical review panel used a case definition similar to that used in the US Public Health Service Cooperative Surveillance Study of 1971 to 1973[8]:

- Serum aspartate aminotransferase (AST) level at least five times the laboratory's normal level, or clinical symptoms likely due to hepatitis—jaundice, abdominal pain, nausea, vomiting, malaise, fever, headache, arthralgias, and myalgias.
- No evidence of other causes of hepatitis: blood tests positive for viral hepatitis, liver biopsies indicating hepatitis from toxins other than isoniazid, or reports of exposures to possibly fatal hepatotoxins near the time of diagnosis.

The panel assessed all available information, including the presence or absence of reported risk factors for isoniazid hepatitis, and classified cases as probable (death was likely due to isoniazid hepatitis), possible (consistent with isoniazid hepatitis, but other causes were possible), or unverifiable. High serum aminotransferase levels and tests negative for hepatitis B surface antigen (HBsAg) were generally necessary for a case to be judged probable. If the data were insufficient to exclude other causes (where only a death certificate was available) the case was judged unverifiable. In the few instances where panel members disagreed about case classification, the majority opinion ruled.

Results

Report of Cases

Authors of published articles and health department staff members reported 108 possible cases of fatal isoniazid-related hepatitis from 1970 to 1992. No state health department had comprehensive machine-retrievable records for identifying suspected cases, and manual searches to identify cases were rarely feasible because of the large volume of records. Therefore, the case-finding effort largely depended on the "institutional memory" of the health department staff. Our search uncovered considerably fewer cases than the 177 reported by others,[28] primarily because these authors included suspected cases from FDA Adverse Reaction Reports and from the National Center for Health Statistics mortality tapes (from which we could obtain no additional information). We also found that some of the previously reported suspected cases were ineligible for various reasons—such as nonfatal cases, duplicate reports, and suicide. In addition, previously reported suspected cases that were unknown to health department staff are excluded from our count, and several recent suspected cases not included previously are included here.

Descriptions of some suspected cases were published in more than one report. Several published reports described suspected cases that occurred in Maryland[6,8,30,31] and California.[22,31-34] Moreover, one of six cases reported jointly[6,8,30] had been described by others.[5,31] We obtained at least some records for 37 of the 49 published cases and for 39 additional suspected cases, for a total of 76 (70%) of the 108 suspected cases. The two most common reasons for failing to obtain documentation were the unavailability of the suspected case's name and the purging of old medical records. In at least five instances, ongoing lawsuits prevented our access to medical records.

Of the 76 suspected cases with documentation, 5 were ineligible: 2 had been treated with several antituberculous drugs, 2 had active tuberculosis, and 1 had no documented isoniazid exposure. The medical review panel therefore evaluated 71 suspected cases. A total of 39 deaths (55%) were judged as probably due to isoniazid hepatitis, 23 deaths (32%) were judged as possibly due to isoniazid hepatitis, and for 9 deaths (13%) the diagnosis was unverifiable.

Region IX of the CDC (Arizona, California, Hawaii, and Nevada) had the largest reported number of probable and possible cases, with 20 (32% of the 62 cases); all but 1 of these cases were from California. Of the 20 California cases reported earlier,[22] 11 were considered probable, 3 were possible, 2 were ineligible, and 4 had no available records. Region III (Delaware; Washington, DC; Maryland; Pennsylvania; Virginia; and West Virginia) and Region IV (Alabama, Florida, Georgia, Kentucky, Mississippi, North and South Carolina, and Tennessee) each had

13 cases, and no other CDC region reported more than 5 cases.

Characteristics of Cases

Three cases were known to have received isoniazid preventive therapy in the private sector; health departments apparently prescribed preventive therapy for all other cases. Table 1 shows the age and sex of the 39 probable and 23 possible cases. For probable and possible cases combined, 50 (81%) were female. Almost 80% of cases (49) were among non–Hispanic blacks or Hispanics (Table 2). For the 35 cases (56%) with a known birthplace, about half were foreign born (Table 3).

TABLE 1.—*Age and Sex of Probable and Possible Cases of Fatal Isoniazid Hepatitis, 1970 to 1992*

Sex	Age, yr	Probable Cases, No.	Possible Cases, No.	Total Cases, No. (%)
Female	0-14	1	1	2 (4)
	15-34	10	2	12 (24)
	35-64	16	14	30 (60)
	65+	5	1	6 (12)
	Total female	32	18	50 (100)
Male	0-14	2	0	2 (17)
	15-34	1	2	3 (25)
	35-64	4	2	6 (50)
	65+	0	1	1 (8)
	Total male	7	5	12 (100)

Details of Isoniazid Preventive Therapy

Figure 1 shows the duration of isoniazid preventive therapy before the onset of hepatitis symptoms. Of the cases, 53 (85%) took isoniazid for 30 weeks or fewer before the onset of symptoms, and the median duration of isoniazid preventive therapy before symptoms began was 16 weeks. Of the 62 patients, 5 (8%) were known to have taken isoniazid intermittently during their course of preventive therapy, and 3 had previously received isoniazid preventive therapy.

TABLE 2.—*Race-Ethnicity of Probable and Possible Cases of Fatal Isoniazid Hepatitis*

Race-Ethnicity	Probable Cases, No.	Possible Cases, No.	Total Cases, No. (%)
White, non–Hispanic	7	5	12 (19)
Black, non–Hispanic	16	15	31 (50)
Hispanic	16	2	18 (29)
Asian	0	1	1 (2)
Total	39	23	62 (100)

TABLE 3.—*Foreign and US-Born Probable and Possible Cases of Fatal Isoniazid Hepatitis*

Birthplace	Probable Cases, No.	Possible Cases, No.	Total Cases, No. (%)
Foreign	14	5	19 (31)
United States	6	10	16 (26)
Unknown	19	8	27 (44)
Total	39	23	62 (100)

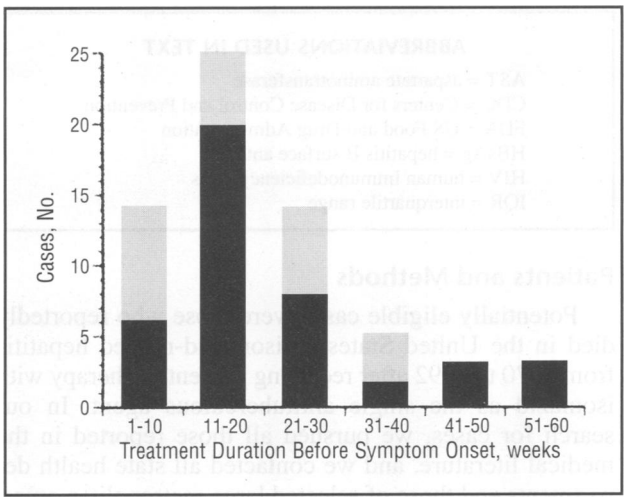

Figure 1.—The duration of isoniazid therapy in weeks before the onset of hepatitis symptoms is shown for probable **(shaded bars)** and possible **(black bars)** cases.

Among the 57 cases with data on the duration of therapy, treatment was continued as long as three months after the onset of symptoms (Figure 2). For two cases, however, isoniazid therapy reportedly ended before the onset of symptoms, and in an additional five cases (9%), therapy was reportedly stopped on the day symptoms began (Figure 2 does not include these 7 cases). In six of the cases (11%) shown in Figure 2, therapy was ended within three days of the onset of symptoms.

The monitoring of patients for adverse medication reactions was variable. For one possible and three probable cases (all occurring before 1982), follow-up was done once every three months. In contrast, 26 cases (42%) were monitored at least monthly; of these patients, 6 were younger than 35 years.

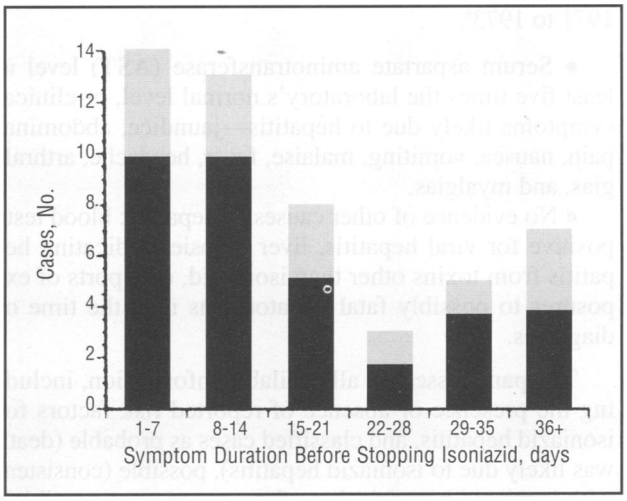

Figure 2.—The duration of hepatitis symptoms in days before stopping isoniazid therapy is shown for probable **(shaded bars)** and possible **(black bars)** cases. In addition, 5 patients stopped therapy on the day symptoms started, and 2 stopped before symptoms began.

Possible Contributing Factors

Because some medical records were incomplete, patients may have had contributing factors that did not appear in their charts. Thus, the reported numbers likely underestimate the actual numbers. In 14 cases (23%), the patients drank moderate to excessive amounts of alcohol or had a history of alcohol abuse. In 28 cases (45%), the patients were taking either possibly hepatotoxic drugs or drugs that could have exacerbated the hepatotoxicity of isoniazid. Possibly hepatotoxic drugs reported for at least two cases included acetaminophen (6 cases); aspirin (4 cases); hydrochlorothiazide (4 cases); and erythromycin, tetracycline, amitriptyline, and phenytoin (2 cases each).

No patients were known to have underlying disease associated with liver dysfunction or to have long-term exposure to environmental hepatotoxins. With the exception of one patient for whom the HBsAg result was unknown, all probable cases had negative HBsAg tests. Among possible cases, 13 were negative for HBsAg, 9 had unknown results, and 1 was positive. Hepatitis A immunoglobulin M antibodies were tested in 18 (46%) probable cases and in 3 (13%) possible cases; all tests were negative. Hepatitis C serologic testing was done for one probable and one possible case and was negative in both instances. The only case known to have been tested for HIV infection had a negative result.

Four women were pregnant at the time of starting isoniazid preventive therapy. In addition, a 23-year-old woman started isoniazid therapy when she was six months postpartum. She was observed monthly, hepatitis symptoms developed during the last month of the planned six-month course, and she continued isoniazid for three weeks after the onset of symptoms.

Clinical Course

Among the 60 probable and possible cases with available data about symptoms, 54 patients (90%) had jaundice on presentation and 30 (50%) presented with nausea. Other common symptoms at presentation included vomiting (25 [42%]), anorexia (23 [38%]), abdominal pain (22 [37%]), and dark urine (21 [35%]). Fifteen patients or fewer presented with changes in mental status, acholic stools, fever, or fatigue.

We could sometimes obtain only a single liver function test result, and that measure may not have corresponded to the patient's peak level. Furthermore, we often did not know the laboratory-specific normal ranges for aminotransferase levels. Nonetheless, the median peak reported AST level was 1,230 units (interquartile range [IQR], 636 to 2,478) in women (that is, 25% of women had levels below 636, and 25% had levels above 2,478) and 1,447 units (IQR, 1,200 to 3,455) in men. The median peak total serum bilirubin level was 28 mg per dl (480 μmol per liter) (IQR, 21 to 35 [360 to 600 μmol per liter]). The median time between the onset of symptoms and death was 32 days (IQR, 24 to 48). For the 21 cases with available information, the median liver weight at death was 600 grams, and 32 (89%) of the 36 cases with autopsy reports had histologic features of hepatic necrosis or acute yellow atrophy. In only 11 of the 43 cases (26%) with death certificates was isoniazid mentioned as a factor contributing to the death.

TABLE 4.—*Appropriateness of Isoniazid Preventive Therapy Among Combined Probable and Possible Cases of Fatal Isoniazid Hepatitis*

Treatment Period	Appropriate Therapy, No.	Inappropriate Therapy, No.	Insufficient Data, No.
1970	1	0	0
1971-1973	3	0	15*
1974-1983	20	5	4
1984-1986	5	0	1
1987-1990	8	0	0

*In 13 cases, participants were from Maryland in the 1971-1973 US Public Health Service study, and data were not available concerning indications for isoniazid prophylaxis.

Appropriateness of Isoniazid Preventive Therapy

Six different sets of recommendations for isoniazid preventive therapy were in effect during the study period.[11-16] Table 4 shows the number of cases occurring in each of the five periods and the authors' judgment concerning the appropriateness of isoniazid preventive therapy according to the guidelines in effect at the time. All patients received appropriate doses of isoniazid. The four deaths in women who were pregnant when isoniazid therapy was started all occurred in the 1980s when the guidelines in effect recommended against starting isoniazid preventive therapy during pregnancy. One 38-year-old woman continued to receive isoniazid despite two negative tuberculin skin tests because she was a tuberculosis contact. Another woman had previously received medication for a year as a participant in a Public Health Service study in 1964—indicating that she may have been unnecessarily retreated with isoniazid in 1985 for a 20-mm tuberculin reaction. The 1964 medication, however, was not definitely identified in the medical records as isoniazid, so it was not possible to judge the appropriateness of the treatment that led to her death.

Discussion

In a large eastern European clinical trial,[9] isoniazid preventive therapy increased the risk of acute hepatitis by fivefold, and the rate of fatal isoniazid hepatitis was 14 per 100,000 person-years. Estimates of the risk of death from isoniazid hepatitis vary considerably, however, and are affected by the characteristics of the population studied and by the degree of clinical vigilance that patients receive while taking isoniazid. In the Public Health Service study of 1971 to 1973, the rate of fatal isoniazid hepatitis was 55 per 100,000 person-years,[8] but the unexpectedly large number of deaths may have been related to local environmental factors in Baltimore, Maryland.[35]

A lack of reliable denominator data has precluded making accurate estimates of the risk of fatal isoniazid hepatitis in the general population.[27] Snider and Caras, however, estimated that at least 1,084,760 persons began isoniazid preventive therapy in the United States during 1972 to 1988 and at least 655,867 completed therapy.[28]

Assuming that the 46 fatal cases treated in the public sector during 1972 to 1988 that we identified represented the totality of cases of fatal isoniazid hepatitis from that population, the estimated rate of fatal isoniazid hepatitis was no greater than 4.2 per 100,000 persons beginning therapy and no greater than 7 per 100,000 persons completing therapy. The estimated rates for 1984 to 1988—during which time routine monitoring of hepatic enzyme levels was recommended for persons older than 35 years of age—were 1.7 per 100,000 starting therapy and 2.9 per 100,000 completing therapy.

Although recent case series have emphasized the dangers of isoniazid preventive therapy,[22,23,36] decision analysis suggests that the benefits of isoniazid preventive therapy outweigh the risks,[36] particularly when considering the additional benefits of preventing the spread of infection to others.[35] But without accurate data concerning the risk of fatal hepatitis as a result of isoniazid preventive therapy, decision analyses should be interpreted with caution. Rose and colleagues, for example, assumed that the risk of death from isoniazid preventive therapy in persons younger than 35 years of age is nil, which is not supported by our data.

Among the 28 fatalities in cases from 15 to 50 years of age, only 5 were men. In the absence of good denominator data, this finding is difficult to interpret, but the high proportion of women in this age group among the cases suggests that women of childbearing age may be at higher risk than men for death from isoniazid hepatitis.

Of the cases, 26 (42%) were monitored monthly in accordance with current recommendations; 6 of these were younger than 35 years and thought to be at low risk for isoniazid hepatitis. Furthermore, 23 patients (38%) stopped taking isoniazid within a week of the development of symptoms of hepatitis, suggesting that a substantial proportion of cases had a fatal outcome despite appropriate monitoring. The relatively large proportion of deaths that occurred among those younger than 35 years is consistent with the findings of Snider and Caras.[28] The current guidelines, which do not advise routine monitoring of hepatic enzymes for those younger than 35 years,[17] may need to be reconsidered in light of the relatively large proportion of patients in this series who were young and who died despite stopping the medication soon after symptoms developed.

This case series is limited by incomplete case ascertainment. We have calculated fatality rates by dividing the number of cases treated in the public sector by the approximate number of persons who, according to Snider and Caras, received isoniazid preventive therapy in the public sector,[28] but these estimates should be interpreted with caution. Almost all the cases we identified had received their care in the public sector, which suggests that we may have failed to identify additional cases from the private sector. For example, during our search we were unaware of some of the recently reported cases associated with liver transplant units in New York.[24] Manufacturers of isoniazid have estimated that half of their sales are to private sources,[28] although the proportion used for preventive therapy is unknown. We were reminded many times while collecting the clinical data that the fear of litigation is common; health care professionals may be reluctant to attribute a patient's death to prescribed therapy. The obstacles to reporting iatrogenic illness are great, and we expect that we underestimated the actual number of deaths from isoniazid hepatitis. Furthermore, the cases we investigated had previously been subjected to sometimes rigorous scrutiny, suggesting that some actual cases may have been rejected by others on the basis of having other identified risk factors for hepatitis. Nonetheless, many of our health department contacts were emphatic that if a case had occurred, they would have known about it.

We attempted to collect data from each state regarding the total number of persons treated annually with isoniazid preventive therapy, and we were struck by the lack of organized systems for collecting such data. The United States has no coordinated system for reporting fatal reactions to isoniazid preventive treatment. The FDA has the responsibility for monitoring drug toxicity, but only 2 of the 20 deaths reported by Moulding and co-workers had been reported to the FDA before the authors' investigation.[22] Death certificates also appear to be an insensitive means of detecting cases. The burden of proof for the safety of preventive programs is high, and the comprehensive national immunization toxicity surveillance program could serve as a model for a similar program to monitor tuberculosis preventive therapy.

In summary, isoniazid preventive therapy poses a dilemma for physicians. Tuberculosis incidence rates are rising, isoniazid prevents active tuberculosis in infected persons, and no other drug can effectively replace isoniazid. A small proportion of patients experience serious hepatotoxicity from isoniazid, however. Adherence to isoniazid preventive therapy guidelines apparently reduces, but does not eliminate, the risk of fatal isoniazid-related hepatitis. Although the risk is low, careful patient selection, education, and monitoring are critical for minimizing that risk.

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