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CLINICAL INQUIRIES FROM THE FAMILY PRACTICE INQUIRIES NETWORK

Are liver function tests required for patients taking isoniazid for latent TB?

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EVIDENCE-BASED ANSWER

Routine liver function test monitoring is not required for all patients on isoniazid therapy for latent tuberculosis (TB) infection (strength of recommendation: **B**, based on case series). No clinical trials have studied the potential risks and benefits of routinely monitoring liver function tests for all patients taking isoniazid for latent TB infection. Data from 2 case series suggest that routine liver function test monitoring leads to withdrawal of isoniazid prophylaxis from about 6% of patients because of abnormal lab results.[1,2] This is 10 to 60 times the hepatitis rate found in case series using a symptom-based monitoring strategy.[3,6] Data are insufficient, however, to conclude that routine liver function test monitoring leads to a lower rate of fatal isoniazid hepatitis compared with a strategy of symptom-based screening. Given that complete recovery from nonfatal hepatitis is the rule, and that patients withdrawn from isoniazid prophylaxis remain at risk for developing active tuberculosis, current evidence does not support routine liver function test monitoring for all patients.

EVIDENCE SUMMARY

Several large population-based case series have tried to define the incidence of isoniazid-induced hepatitis and fatal hepatitis. Because these series differed in patient selection, diagnostic criteria for hepatitis, and toxicity monitoring strategies, and because their data span decades, they provide limited insight. Data from 6 large case series[1,3-7] and 1 pooled compilation of published and unpublished reports[8] are summarized in the **Table**.

Two studies[1,2] that defined hepatitis as asymptomatic liver function test elevation (>5 times normal) on monthly screening found a 6% to 6.4% incidence of hepatitis, a rate 10 to 60 times higher than 4 case series[3-6] that relied on symptom-based monitoring. A pooled analysis of more than 200,000 patients receiving isoniazid prophylaxis and monitored according to 1983 American Thoracic Society guidelines reported an intermediate hepatitis rate (1.2%) and only 2 deaths.[8] Mortality from isoniazid hepatitis is rare, whichever monitoring

strategy is selected. Some deaths attributed to isoniazid prophylaxis may also have had other contributing causes, such as unrecognized hepatitis C; most cases and deaths reported in these large series occurred before testing for hepatitis C became available in 1991.

Symptom-based monitoring strategies require stopping isoniazid promptly if symptoms of hepatotoxicity develop. In a series of 62 fatal cases of probable or possible isoniazid hepatitis, 42% had been monitored at least monthly for symptoms, and 38% stopped isoniazid within 1 week of symptom onset.[9] Seven of the 8 patients receiving a liver transplant following the development of fulminant, isoniazid-related hepatitis continued to take the drug for a least 10 days after onset of symptoms of hepatotoxicity.[10]

Several series report increasing hepatitis risk with advancing age.[1,3,5,6] In 1 series,[3] rates were 3/1000 in those aged 20 to 34 years, 12/1000 in those aged 35 to 49 years, 23/1000 in those aged 50 to 64 years, and 8/1000 after age 65.

INH hepatitis incidence and mortality rates: summary of the largest case series

Study	Time period	Monitoring strategy	Hepatitis definition	No. of patients	No. of hepatitis cases	No. of fatal cases mortality rate
Byrd[1]	~early/ mid 1970s	Monthly symptom and LFT screening	AST >5x normal, with or without symptoms	1000	64 (6.4%)	0
Salpeter[8]	1983- early 1990s	Presumed to follow 1983 ATS guidelines[a]	Not defined	202,497	2,459 (1.2%)	2 (0.001 %)
Kopanoff[3]	July 1971 to Nov. 1972	Monthly symptom-based screening	AST ≥250 Karmen units or ALT>AS	13,838	92 (0.66%)	8 (0.06%)

			T, and no other cause			
IUATCP[4]	mid-1970s	Every-4-week symptom-based screening	Not defined	20,840	95 (0.5%)	3 (0.014 %)
Dash[4]	Jan. 1973 to June 1977	Monthly symptom based screening	Jaundice, scleral icterus, or “hepatitis” notation	5300	15 (0.37%)[b]	1 (.019%)
Nolan[6]	Jan. 1989 to 1 December 1995	Monthly symptom-based screening	AST >5x normal with symptoms, and no other cause	11,141	11 (0.1%)	0
LoBue[7]	July 1999 to Nov. 2002	Monthly clinical monitoring, routine LFTs for patients >34 before 2000	LFTs >3x normal with symptoms, or LFTs >5x normal without symptoms	3,788	10 (0.3%)	0

[a] Withhold treatment in presence of active liver disease, limit prophylaxis of patients aged >35 to those at highest risk of developing active disease, baseline and periodic LFTs for those over 35, discontinue isoniazid if transaminases exceed 3 to 5 times normal.

[b] Calculation based on life-table analysis, because of high dropout rate during treatment LFT, liver function test; AST, aspartate transaminase; ALT, alanine transaminase; IUSTCP, International Union Against Tuberculosis Committee on Prophylaxis

RECOMMENDATIONS FROM OTHERS

The Centers for Disease Control and Prevention (CDC) and the American Thoracic Society joint guidelines for the treatment of latent TB infection state that baseline laboratory testing is not routinely indicated, even for persons aged >35 years, but may be considered for patients who are taking other hepatotoxic medications or have chronic medical conditions.[11]

Baseline measurements of bilirubin and aspartate transaminase (AST) or alanine transaminase (ALT) along with monthly liver function test monitoring are recommended for patients with pre-existing liver disease, patients at risk for chronic liver disease, patients with HIV infection, pregnant or postpartum women, and regular users of alcohol. All patients should be evaluated at least monthly for symptoms of hepatitis, and liver function tests should also be obtained for patients with symptoms compatible with hepatotoxicity. The guideline suggests that isoniazid be stopped if liver function tests exceed 5 times the upper limits of normal, or 3 times the upper limits of normal if the patient is symptomatic. The *Canadian Tuberculosis Standards* (5th ed, 2000) recommend baseline AST before isoniazid preventive therapy is started, and regular monitoring in those with pre-existing liver disease, a history of ethanol abuse, or age ≥35 years.[12]

CLINICAL COMMENTARY

Patients need to understand risks and benefits of TB treatment

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As the number of immigrants increases, FPs will see more patients at high risk for TB. Patients whose risk of developing active TB exceeds the risk of isoniazid toxicity should be tested (targeted testing). It is challenging to ensure an asymptomatic patient completes a 9-month course of therapy while undergoing monthly monitoring for symptoms of isoniazid toxicity. Overall, only 60% of patients complete a full course of isoniazid. Clinical and public health systems that make it easier for patients to follow-up can enhance compliance.

Patients need to understand the benefits of treatment and the symptoms of isoniazid toxicity. The CDC recommends clinical monitoring without routine blood testing for patients of any age without additional risk factors for isoniazid hepatitis. Excessive monitoring can lead to premature discontinuation of therapy because 10%–20% of patients develop some liver function test elevation. The CDC has an excellent course on

the basics of latent TB testing and treatment (at **www.phppo.cdc.gov/phtn/tbmodules/Default.htm**). Patient education materials and risk assessment and monitoring forms can be obtained from state health departments.

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