Isoniazid Toxicity in Health Care Workers

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The toxicity of isoniazid chemoprophylaxis was assessed in 83 health care workers (HCWs) receiving a 6-month course, in whom clinical toxicity and liver function were monitored. Thirty-four HCWs (41%) developed an adverse event; in 26 (76%), toxicity was sufficiently severe to require cessation of treatment. Of the total, liver function test abnormalities (serum alanine transaminase levels more than two times normal) were evident in 14 subjects, with 8 requiring cessation of therapy. Other symptoms reported included malaise, nausea with associated anorexia, arthralgia, and rash. Mean time to development of symptoms was 3 weeks (range, 0.5–6 weeks), with the mean age of those with toxicity not differing significantly from those without (38 vs. 39 years). The high rate of toxicity seen in this study is sufficiently notable that we advocate the use of monthly liver function testing and frequent review in those receiving isoniazid prophylactic therapy.

Tuberculosis is a well-recognized occupational risk for health care workers (HCWs) [1]. Although rates of tuberculosis declined steadily since the 1950s, HIV infection and multidrug-resistant strains of Mycobacterium tuberculosis have resulted in a resurgence in the last decade, with nosocomial transmission of tuberculosis to HCWs recently reported [2]. Effective infection control measures can greatly decrease nosocomial transmission, but this alone will not eliminate the risk for HCWs. Therefore, other means of reducing occupationally acquired tuberculosis remain important.

Isoniazid (isonicotinic acid hydrazide) has been shown to be effective in preventing the development of active disease among asymptomatic, infected persons by 60%–95% [3, 4]. Despite the benefits of preventive therapy, isoniazid is not widely applied because of missed opportunity, fears of toxicity, and poor adherence [5]. To assess the toxicity of isoniazid, we prospectively monitored HCWs receiving isoniazid chemoprophylaxis in a public hospital undergoing a comprehensive tuberculin skin-testing program.

Methods

As a part of an Occupational Health and Safety program, HCWs were offered a tuberculin skin test (TST) according to Australian guidelines [6]. A strong positive reaction was defined as ≥15 mm in subjects with prior bacille Calmette-Guérin vaccination and ≥10 mm in those without such a history [7]. All HCWs with strongly positive TST results were screened by chest radiography and were seen by a physician for further counseling.

Isoniazid therapy was discussed with each subject attending for physician follow-up. Subjects were informed of potential benefits and toxicities of isoniazid and were encouraged to make individual decisions about whether to commence therapy. Persons with a history of heavy alcohol intake or chronic liver disease were not offered isoniazid prophylaxis. Similarly, all subjects were counseled to minimize their alcohol intake should they wish to proceed with isoniazid prophylaxis. Specific serologic studies for hepatitis B and C viruses and HIV were done if risk factors for acquisition of these viruses were identified.

Those HCWs considering the commencement of isoniazid had a baseline serum liver function test (LFT) done to assess the existence of underlying hepatic inflammation. If LFT results were normal, a 6-month course of isoniazid, 300 mg/day, and pyridoxine, 25 mg/day, was prescribed. Subsequently, further LFTs were done at monthly intervals. If these were abnormal, serologic studies for hepatitis A, B, and C viruses were done to exclude a viral cause of liver dysfunction. At each monthly clinical review, information was obtained regarding the HCWs’ adherence with isoniazid therapy and whether they had noted any symptoms, including those that could be potentially isoniazid-associated.

Results

A total of 878 HCWs had TSTs done, 89% of whom had a definite history of bacille Calmette-Guérin vaccination. Overall, 299 (34%) of 878 had a strong positive reaction. Of these, 291 with a history of bacille Calmette-Guérin vaccination had a TST result of ≥15 mm, and an additional 8 who had not been vaccinated with bacille Calmette-Guérin had a TST result of ≥ 10 mm. Ten (3%) of the 299 HCWs had chest radiographic evidence of former tuberculous infection, and 1 subject had a pulmonary infiltrate potentially consistent with active tubercu-
Table 1. Adverse events experienced by HCWs while receiving isoniazid preventive therapy.

<table>
<thead>
<tr>
<th>Adverse event*</th>
<th>All HCWs (n = 83)</th>
<th>HCWs ceasing therapy</th>
<th>Mean time of onset, w (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total adverse events</td>
<td>34 (41)</td>
<td>26 (100)</td>
<td>3 (0.5–6)</td>
</tr>
<tr>
<td>Abnormal LFTs</td>
<td>14 (17)</td>
<td>8 (31)</td>
<td>4 (3–6)</td>
</tr>
<tr>
<td>Malaise</td>
<td>14 (17)</td>
<td>8 (31)</td>
<td>3.5 (2–6)</td>
</tr>
<tr>
<td>Nausea, vomiting, anorexia</td>
<td>10 (12)</td>
<td>7 (27)</td>
<td>3 (2–6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4 (5)</td>
<td>4 (15)</td>
<td>3 (0.5–6)</td>
</tr>
<tr>
<td>Confusion/emotional lability</td>
<td>2 (2)</td>
<td>2 (8)</td>
<td>2.5</td>
</tr>
<tr>
<td>Rash/itch</td>
<td>2 (2)</td>
<td>2 (8)</td>
<td>3</td>
</tr>
<tr>
<td>Fever (≥38°C)</td>
<td>2 (2)</td>
<td>2 (8)</td>
<td>2.5</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (2)</td>
<td>1 (4)</td>
<td>3</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) or mean (range), as applicable. HCW = health care worker; LFT = liver function test.

* Some HCWs had multiple symptoms.
1 For those HCWs ceasing therapy.
2 Peak alanine aminotransferase readings were noted after mean of 6 weeks (range, 4–8 weeks).

This prospective study of isoniazid chemoprophylactic therapy reveals a relatively high incidence (34 [41%] of 83) of side effects among HCWs receiving this treatment. Of these, 26 (76%) had symptoms sufficiently severe to require cessation of treatment. Liver function test abnormalities of clinical significance were noted in 17% of cases, with 57% of these (6% overall) requiring cessation of therapy. Notably, subjects with significantly elevated serum alanine aminotransferase levels had minimal symptoms. Although isoniazid-induced asymptomatic hepatitis has been reported in up to 10%–20% of subjects and overt hepatitis in 1%, its incidence is generally reported to be age-related, particularly in those >35 years old [8]. Our findings reveal a greater incidence of toxicity than these historical data, and the notable lack of symptoms among those HCWs with the most severe hepatitis reinforces the importance of regular monitoring of hepatic function in all isoniazid-treated persons.

Less severe symptoms, however, accounted for more treatment withdrawals. Importantly, symptoms often regarded as insignificant (e.g., malaise, nausea, arthralgia, and myalgia) were prominent in our study population and were considered to be of sufficient severity to require isoniazid cessation in the majority of subjects, despite patients’ motivation to complete treatment.

The reasons for the high rate of reported side effects remain uncertain and are probably multifactorial. Unfortunately, the lack of a control group in this study limits the certainty with which all reported adverse reactions can be directly attributed to isoniazid, although this seems very likely. Nevertheless, this rate of toxicity is somewhat higher than the 11.4% reported by Camins et al. [9] in their retrospective study of 105 HCWs receiving isoniazid. In comparison, the higher rate of toxicity that we noted may have been due to the prospective nature of our study in which liver function and clinical progress were monitored prospectively at monthly intervals.

However, the fact that a reasonably large number of HCWs considered their symptoms to be of sufficient severity to cease treatment suggests that other factors may also be involved. The predominance of females, most of them of child-bearing age, in our study population suggests the possibility of hormonal influences on isoniazid toxicity. Unfortunately, we did not collect data on menstrual cycles or the use of the oral contraceptive pill in our cohort. Finally, we cannot exclude some overreporting of subjective symptoms among HCWs who were working closely together and discussing their problems with each other. However, the rate of objective adverse events argues against this constituting the main explanation.
These results have important implications for isoniazid prescribing and clinical monitoring. Preventive therapy with isoniazid has an important role, and guidelines for such therapy have been defined [10]. Nevertheless, the relatively high rate of symptomatic and asymptomatic toxicity noted in this study is worth considering when prescribing isoniazid prophylaxis, and it is sufficiently notable that we advocate the use of monthly liver function testing and frequent review in those receiving isoniazid prophylactic therapy, regardless of their clinical state.

References