Monitoring Preventive Therapy Patients for Liver Disease as Well as Compliance

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An apparently increasing incidence of isoniazid-associated hepatitis concurrent with interest in the problem has led to the universal teaching that patients on isoniazid preventive therapy must be carefully monitored for liver disease. This teaching has been reinforced and endorsed in a recent report of the tuberculosis advisory committee and special consultants to the director of the Center for Disease Control; this report, in turn, led to an American Thoracic Society statement concluding that the use of isoniazid with appropriate safeguards must be based on a comparison of the benefit of preventive therapy with the risk of hepatic injury and, therefore, should be used when necessary, under careful control and follow-up. In New York City, with increasing use of the tuberculin skin test leading to increased numbers of patients receiving this treatment in nurse-operated clinics, a new control form and protocol were designed. These insure that all individuals on preventive therapy are carefully monitored for liver disease as well as compliance in taking the drug. This system also insures the safeguards alluded to, as well as increasing concern and awareness among the health professionals in prescribing the treatment.

Isoniazid is the cheapest, best, and by far the most widely used antituberculosis drug. It is thought by many to be an important factor in the decline of tuberculosis, whether used as treatment for the disease in combination with other drugs, or singly as preventive therapy in those infected with the tubercle bacillus.

Since its introduction in 1952, isoniazid has been shown to be safe and relatively free of adverse side effects.1 However, more recently, various observers have noted what appears to be an increasing incidence of hepatic disease associated with isoniazid.2 This is thought to be due to its increasing use as the single agent in asymptomatic individuals for preventive therapy in tuberculosis infection.

At first, isoniazid-associated hepatitis was not of much concern. Its suspected existence was taken by some health jurisdictions as a reason to increase the number of visits of patients on treatment or preventive therapy with this drug to one per month or more to insure better follow-up.

More recently, it has been noted that fatal cases of isoniazid-associated hepatitis have occurred in patients under surveillance for this complication.2-7 There is some evidence that some of these patients may have continued isoniazid after having manifested symptoms of hepatitis.1,8 A recent report9 and statement,10 prepared after a thorough review of the entire isoniazid-associated hepatitis picture, reiterated the previous recommendation7 of providing isoniazid for persons infected with Mycobacterium tuberculosis who are at high risk of developing tuberculosis provided that the isoniazid is used "with appropriate safeguards" that include interviewing of patients and an evaluation by clinical means at monthly intervals. Tuberculin reactors over the age of 35 with no other risk factors are no longer routinely recommended for preventive therapy. A standardized form to insure alertness to all signs and symptoms, to expedite the interview process, and to provide for standardized data collection was also suggested.10

In January 1973 the city of New York abolished all walk-in screening chest x-ray units, replacing them with walk-in tuberculin testing units. This has led to increased numbers of persons on isoniazid preventive therapy well beyond the 10,000 receiving this treatment in early 1973.

In order to tighten up control of these patients, thus implementing the appropriate safeguards where many patients are seen for follow-up by nurses and paramedical personnel, we introduced and used a special protocol and new form for these patients. Our procedures and chart form, which is introduced in this report, permits the New York City Health Department to carefully monitor their patients, insuring the use of isoniazid when indicated,
while assuring the patients of the closest possible surveillance for compliance as well as hepatitis.

All persons under the care of the New York City Health Department who have a positive tuberculin test (utilizing the Mantoux technique with 5 tuberculin units of purified protein derivative of tuberculin or an equivalent commercial preparation) are given a chest x-ray examination. If no active tuberculous disease is found, they then consult with a health department physician who determines, with the patient in attendance, if preventive therapy is indicated. All patients below age 30** and those listed in groups 1 to 4 of the American Thoracic Society, regardless of age, are strongly offered preventive therapy.

The listing of the American Thoracic Society for various groups in order of priority for receiving preventive therapy*9,10 is as follows:
1. Household members and other close associates of persons with recently diagnosed tuberculous disease
2. Positive tuberculin reactors with findings on the chest roentgenogram consistent with nonprogressive tuberculous disease, without positive bacteriologic findings, and without a history of adequate preventive therapy

**As stated earlier, the recent American Thoracic Society statement has changed recommendations to give preventive therapy to all persons below age 35.9,10

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<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>Date of Interview</th>
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<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
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<tr>
<td>Urine darker color than usual</td>
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<tr>
<td>Stools lighter color than usual</td>
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<td>Yellow skin or eyes noted by patient (ask and observe)</td>
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<td>Nausea or vomiting more than two (2) days</td>
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<td>Unusual weakness or fatigue lasting more than three (3) days</td>
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<tr>
<td>History of elevated temperature for more than three (3) days without a cold or other clear reason</td>
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<tr>
<td>Sustained loss of appetite</td>
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**OTHER SYMPTOMS**

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Advice given to:
- Told to contact nurse or M.D. again on (date)
- Referred for liver work-up (specify arrangements)
- Refer to: (Core Clinic, P.T.C. review; institution care) - specify

**REMARKS**

- Drugs dispensed and amount
- Revisit date (within 4 weeks)

**INTERVIEWED BY:**

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**Figure 1.** Record used for monitoring patients on isoniazid preventive therapy.

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CHEST, 68: 2, AUGUST, 1975

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**MONITORING PATIENTS FOR LIVER DISEASE**

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3. Newly infected persons
4. Positive tuberculin reactors in the following special clinical situations:
   a. Prolonged therapy with adrenocorticoids
   b. Immunosuppressive therapy
   c. Some hematologic and reticuloendothelial diseases, such as leukemia or Hodgkin's disease
   d. Diabetes mellitus
   e. Silicosis
   f. After gastrectomy
5. Other positive tuberculin skin test reactors

The patient is told that there is a slight risk of hepatic reaction to the drug and that he must be seen at no less than monthly intervals for the one year of treatment. If the patient accepts, only one month's supply of isoniazid is given at one time. The subsequent 11 visits are usually in a nurse-operated clinic, where they are monitored by a nurse or physician's associate. Unless complications arise, the patient does not see a physician after his first visit. No follow-up x-ray examination is done in patients who have received a complete course of preventive therapy.

Most authors, in discussing the problem of isoniazid-associated hepatitis, state that close supervision is mandatory, but little has been written on how to carry this out in an era of nurse-directed clinics.
with wider use of preventive therapy. At the New York City Health Department, we introduced a self-contained questionnaire clinic chart (Fig 1). Essentially, the form provides seven questions to insure alertness to all signs and symptoms of hepatic disease, as was suggested by the new statement of the American Thoracic Society on preventive treatment of tuberculosis. These questions are explicitly asked and answered on the chart. If any of the symptoms are present, the drug is stopped, and the patient is referred to a physician who determines if the drug should be stopped permanently or if further work-up should be done, or both. These actions are then noted on the chart. Any other entries are written in a dated note on the reverse side of the form. If a patient is not seen within 30 days of his last visit, the column is left blank, and health aide follow-up can be initiated. This has the added advantage of permitting lapses to be noted at a glance.

A checklist for possible symptoms or side effects of drugs is not a new idea. A recently published study reported that a checklist elicited more nuisance symptoms; the study also noted that known side effects of a drug were more effectively elicited and symptoms not included in a checklist more likely reported if a checklist was not used.

However, our checklist is used by the interviewer, not directly by the patient. Since we are interested in following up the least disturbance in a patient’s health, secondary to his medication, the more positive responses on a checklist, the more to follow up and the less chance of missing a potentially important finding.

This protocol and form has been used in the clinics of the New York City Health Department since January 1973. They have been extremely well accepted by their staff. They have served to make the health department employees and professional personnel aware of and to respect the fact that isoniazid prophylaxis is perhaps the most important tool in tuberculosis control in New York City today, but one that cannot be taken lightly. Monthly clinical evaluation of the patient on preventive therapy is thus standardized, thereby increasing compliance and bettering surveillance for isoniazid-associated hepatitis.

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REFERENCES
9 Isoniazid-associated hepatitis: Summary of the report of the Tuberculosis Advisory Committee and special consultants to the Director, Center for Disease Control. Morbidity Mortality Weekly Rep 23, 1974