Isoniazid Therapy of Primary Tuberculosis in Children

KATHARINE H. K. HSU, M.D., F.C.C.P.*
Houston, Texas

There are millions of children in the world today who have been infected by tubercle bacilli. These children will be a significant source of active tuberculosis of tomorrow. With the advent of a potent antituberculosis drug such as isoniazid (INH), a major attack on this disease must be directed to primary tuberculosis in children.8,9

This paper is a report on a study of 128 children under 36 months of age with positive tuberculin reactions who have been under the care of this service for 12 to 36 months. These young children were selected for evaluation of INH therapy because of the high morbidity and mortality rates of primary tuberculosis at this age period.5-7 The severity of primary infection in this series of cases is indicated by the fact that almost one-half of the patients had already developed manifested forms of active tuberculosis when first seen and that tubercle bacilli were demonstrated in 45 of the 128 cases. The age distribution is shown in Table 1.

Drug therapy consisted of INH and PAS. The dosage of INH was 5 to 10 mg. per kg. of body weight before 1956. Since 1956, the dosage has been raised to 10 to 15 mg. per kg. For miliary disease and meningitis a higher dosage of 20 to 30 mg. per kg. has been used and streptomycin has been given in addition. PAS in the dosage of 200 mg. per kg. has been given as an adjuvant in all cases. Twelve months of continuous drug therapy was considered minimal for the treatment of tuberculosis. Many patients were given longer periods of therapy because of the extent of the disease. Twelve children received for only short periods of time treatment due to lack of cooperation on the part of the parents — Table 2.

Table 3 shows the types of cases and the results of therapy. There were 66 children with normal chest radiographs. None of these children has developed manifested forms of active tuberculosis to date. Forty-two children had segmental or lobar involvement and five had large mediastinal nodes. These types of cases are much more liable to develop tuberculosis at new sites of the body than those with normal chest radiographs.4 However, with therapy none has developed tuberculous complications after 12 to 36 months of follow-up observation. Since the great majority of tuberculous complications occur within one year of the primary infection,6,7 these results indicate that INH therapy is effective in preventing them. This is particularly remarkable in view of the young age and the heavy household contamination of these children. The four patients with miliary tuberculosis recovered uneventfully. None has developed bone or renal tuberculosis. The four cases with meningitis survived, two of whom suffered from mild mental retardation.

*Assistant Professor of Pediatrics, Baylor University College of Medicine, Texas Medical Center. Pediatrician in Charge, City of Houston, Children's Tuberculosis Hospital and Clinic.

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Since the advent of INH, its therapeutic value in primary tuberculosis in children has been studied by prominent investigators in France, Germany, and Greece. In the United States a large-scale controlled study, including the use of placebo, has been conducted under the auspices of the Public Health Service beginning in 1955 with 32 pediatric clinics participating. The observation so far has shown that 80 per cent of the immediate complications of primary tuberculosis can be prevented by INH therapy even at a small dosage of 4 to 6 mg. per kg. a day.

Witte, in his review of 1220 cases of tuberculosis in infants under one year of age, has shown that INH is effective in the prevention of serious complications of primary tuberculosis especially hematogenous disseminations, which usually result in tuberculous meningitis, miliary tuberculosis, and other extra-pulmonary tuberculosis. For the treatment of infants found with generalized tuberculosis upon admission to the hospital, INH has proved more potent than other anti-tuberculosis drugs.
Since effective therapy for primary tuberculosis is now available, it is more than ever regrettable that children today develop the more serious forms of tuberculosis. In many countries today, primary tuberculosis is still prevalent. Even in countries where BCG vaccination is used, many children are still found with positive tuberculin reactions who have never been vaccinated with BCG. In some areas, as many as 50 per cent of the children have been infected as shown by positive tuberculin reactions. The infection is often so severe that many become sick and die. Prevention of serious tuberculous diseases by institution of INH therapy during the early stage of primary infection is a crying need of these children and, therefore, a new responsibility of the physicians. The prevalence and severity of primary tuberculosis in those areas offer the physicians excellent opportunities to further the study of the problems relative to drug therapy of primary tuberculosis.

In countries where the incidence of tuberculosis is low and where BCG vaccination is not in general use, a diligent search for primary tuberculosis by tuberculin testing among the young children is an important strategy in tuberculosis control. In Houston, Texas, even in the poorest districts of the city, the tuberculin index is only 1.3 per cent in the pre-school children. The infection rate is even lower in the general children population. The scarcity of tuberculin reactors in the young children makes them sensitive indicators of the hidden pools of tuberculosis in the community. In this series of cases 83 of the 128 children were from homes in which one or more adults were found to have active pulmonary tuberculosis. In 14 cases active tuberculosis was found among the children's close associates outside the home. Therefore, the finding of these infected children is necessary not only for the early treatment, but also for the detection of unrecognized cases of adult tuberculosis in all associated families.

<table>
<thead>
<tr>
<th>TYPE OF CASES</th>
<th>NO. OF CASES</th>
<th>LATEST EXAMINATION</th>
<th>NON-PULM. COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO X-RAY EVIDENCE</td>
<td>66</td>
<td>20 HILAR CALC. 46 NORMAL LUNGS</td>
<td>0</td>
</tr>
<tr>
<td>LARGE MEDIASTINAL NODES</td>
<td>5</td>
<td>5 RESOLUTION (3 HILAR CALC.)</td>
<td>0</td>
</tr>
<tr>
<td>SEGMENTAL OR LOBAR</td>
<td>42</td>
<td>35 RESOLUTION (11 HILAR CALC.) 7 CONTRACTED SEGMENTS</td>
<td>0</td>
</tr>
<tr>
<td>PLEURISY</td>
<td>1</td>
<td>1 RESOLUTION</td>
<td>0</td>
</tr>
<tr>
<td>PERIPHERAL LYMPHADENITIS</td>
<td>6</td>
<td>4 BIOPSY EXCISION 2 RESOLUTION</td>
<td>0</td>
</tr>
<tr>
<td>MILIARY</td>
<td>4</td>
<td>3 RESOLUTION (1 HILAR CALC.) 1 CONTRACTED SEGMENT</td>
<td>0</td>
</tr>
<tr>
<td>MENINGITIS</td>
<td>4</td>
<td>2 NO RESIDUAL 2 MENTALLY RETARDED</td>
<td>0</td>
</tr>
</tbody>
</table>
Even in communities of low tuberculosis rate, children from tuberculosis homes run great risk of infection. In our experience as high as 70 per cent of them show positive tuberculin reactions. Many of these infected children do not show signs of illness until in the late stage of the disease. In this series of cases fully one-half of those who were found to have large areas of opacity in the chest radiograph had shown no outward sign of ill health. For this reason all children who have been in close contact with a tuberculous adult must be tuberculin tested for the detection of primary tuberculosis. Since it takes several weeks for the tuberculin sensitivity to develop, the negative reactors must be retested within two to three months for conversion of the tuberculin reaction. In our experience periodic tuberculin testing of known contacts is one of the best ways of finding primary tuberculosis in its early stage when INH therapy would do the most good.

For the millions of children who have been infected by tubercle bacilli a new hope is found in isoniazid.

SUMMARY

1. Isoniazid is effective in preventing tuberculous complications, thus minimizing the danger of primary tuberculosis.

2. Isoniazid is a remarkably effective agent for the treatment of all clinical forms of tuberculosis in children.

3. Since effective therapy is now available, every effort should be made to seek out the infected children by routine tuberculin testing so that they may receive the benefit of INH therapy in the early stage of the infection. Special attention should be given to children under 36 months of age because of the high mortality and morbidity rates of tuberculosis at this age period.

4. In countries where tuberculosis incidence is low and where BCG vaccine is not in general use, routine tuberculin testing of young children serves the dual-purpose of early treatment of primary tuberculosis in children and the detection of unrecognized tuberculosis in adults.

RESUMEN

1. La isoniazida es efectiva para prevenir las complicaciones tuberculosas haciendo así mínimo el peligro de la tuberculosis primaria.

2. La isoniazida es un medicamento notablemente eficaz en el tratamiento de todas las formas de la tuberculosis infantil.

3. Puesto que ahora contamos con un tratamiento efectivo, hay que hacer toda clase de esfuerzos para encontrar los niños infectados, usando para ello la tuberculorreaconación a fin de que reciban pronto los beneficios de la INAH al principio de la enfermedad.

Debe darse especial atención a los niños menores de 36 meses debido a la elevada mortalidad de la tuberculosis en esa edad.

4. En los países donde la tuberculosis es poco frecuente y donde la vacuna B.C.G. no es de uso general la prueba de tuberculina, las reacciones tuberculínicas de rutina sirven para el doble propósito de tratar tempranamente la tuberculosis primaria en los niños y para reconocer la tuberculosis ignorada entre los adultos.

RESUMÉ

1. L'isoniazide est efficace pour prévenir les complications tuberculeuses et minimiser ainsi le danger de la tuberculose primaire.

2. L'isoniazide est un produit remarquablement efficace pour le traitement de toutes les formes cliniques de tuberculose chez l'enfant.

3. Puisque nous avons maintenant à notre disposition une thérapeutique efficace, nous devrions faire des efforts pour rechercher les enfants infectés, par les tests courants à la tuberculine, de façon à ce qu'ils puissent recevoir le bénéfice du traitement par l'isoniazide dans le stade précoce de l'infection. Une attention particulière devrait être donnée aux enfants âgés de moins de 36 mois à cause des taux élevés de mortalité et de morbidité par tuberculose à cet âge.

4. Dans les pays où la tuberculose n'a qu'une basse fréquence et où le vaccin B.C.G. n'est pas courant, la détection de la tuberculose primaire chez les enfants et de la tuberculose ignorée chez les adultes...
ZUSAMMENFASSUNG

1. Isoniazid ist wirksam hinsichtlich der Verhütung tuberkulöser Komplikationen und setzt die Gefahr der Primärtuberkulose auf ein Minimum herab.

2. Isoniazid ist eine bemerkenswerte wirksame Substanz zur Behandlung aller klinischen Formen der Kindertuberkulose.


REFERENCES