Analysis of the chemoprophylactic effect on close contacts of patients with active tuberculosis and positive tuberculin skin tests

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Abstract

Objective: The current study analyzed the chemoprophylactic effect of isoniazide on close contacts of patients with active tuberculosis and positive tuberculin skin tests (TSTs).

Methods: A total of 1206 close contacts of patients with active tuberculosis and strongly-positive TSTs were enrolled. The patients had chest X-ray examinations. Patients without tuberculosis and other diseases were divided into the following groups: 90 patients in the prophylaxis group, who were given 300 mg of isoniazid qd (3–5 mg/kg for children) over a 10-month treatment course; and 89 patients in the control group without drug therapy. Both groups were followed for 10 years.

Results: (1) There were 568 patients with negative results and 638 with positive results, including 445 with ordinarily- and moderately-positive results, and 193 with strongly-positive results (a positive rate of 52.9% [638/1206] and a strongly-positive rate of 16.0% [193/1206]). Fourteen tuberculosis patients were identified (tuberculosis detection rate of 1.1%). (2) During the 3-year period of follow-up, there were 4 patients in the prophylaxis group and 12 in the control group who acquired tuberculosis (a morbidity rate of 4.7% [4/84] and 13.4% [12/89], respectively), and the difference was statistically significant ($\chi^2=3.916, P=0.048$). Six patients in the prophylaxis group, all of whom were children, discontinued medication use during the course of treatment due to adverse drug reactions, for an adverse drug reaction occurrence rate of 6.6% (6/90), a medication completion rate of 93.3% (84/90), and a 3-year protection ratio of 64.6%. (3) During the 4–6 year period, there were two patients in the prophylaxis group and three patients in the control group who acquired tuberculosis (a morbidity rate of 2.5% [2/78] and 4.1% [3/73], respectively), two in the prophylaxis group and four in the control group who were lost to follow-up (a loss to follow-up rate of 2.5% [2/80] and 5.1% [4/77], respectively), and the difference was not statistically significant ($\chi^2=0.215, P=0.643$). (4) During the 7–10 year study, there was one patient in the prophylaxis group and two patients in the control group who acquired tuberculosis (a morbidity rate of 1.3% [1/72] and 3.1% [2/64], respectively), and four in the prophylaxis group and six in the control group who were lost to follow-up (a loss to follow-up rate of 5.2% [4/76] and 8.5% [6/70], respectively), and the difference was not statistically different ($\chi^2=0.011, P=0.918; \chi^2=0.176, P=0.675$). (5) Within 10 years, there were 7 patients in the prophylaxis group and 17 patients in the control group who acquired tuberculosis (a morbidity rate of 8.3% [7/84] and 21.5% [17/79], respectively; $\chi^2=4.770, P=0.029$), and 6 in the prophylaxis group and 10 in the control group were lost to follow-up (the loss to follow-up rate was 7.1% [6/84] and 11.2% [10/89], respectively; $\chi^2=0.863, P=0.353$).

Conclusion: Close contacts of patients with active tuberculosis are at high-risk for acquiring tuberculosis. It is safe and effective for patients with strongly-positive TST results to undergo isoniazid chemoprophylaxis for 10 months.

Keywords: Tuberculin, Skin test, Strongly positive, Isoniazid, Chemoprophylaxis

References

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Introduction
Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis*. Tuberculosis has spread worldwide, consumes the social labor force severely, and imposes a heavy economic burden on the patient and the family. China is 1 of 22 countries with a heavy burden of TB, with the number of TB patients ranking second worldwide. Among people ≥15 years of age, the morbidity rate of active TB is 459/100,000, with a morbidity rate of sputum smear-positive TB of 66/100,000 [2]. Patients with sputum smear-positive TB are the main source of infection and TB is spread through the droplet. Tuberculosis is characterized by randomness, and occasional contact and transmission are the main modes of TB transmission [3]. The risk of infection in close contacts of TB-infected patients is increased. We have administered tuberculin skin tests (TSTs) to close contacts of patients with active TB and identified patients with strongly-positive TSTs, initiated isoniazid chemoprevention in an effort to determine the prophylactic effect through follow-up visits over 10 years.

Subjects and methods
Subjects
Between January and December 2003, a total of 1206 close contacts (574 males and 632 females, and 31 children <12 years of age [all of whom were inoculated with Bacillus Calmette-Guerin {BCG}]) with active TB patients were included as study subjects, and included family members, co-workers, and students in the same classrooms or housed in the same dormitories. Among the 1206 subjects, the oldest was 65 years of age and the youngest was 8 years of age, with an average age of 39.04±2.25 years. Subjects with a definite intimate contact history for 4–8 weeks were given TSTs to identify TB patients and those with strongly-positive TSTs, initiated isoniazid chemoprevention in an effort to determine the prophylactic effect through follow-up visits over 10 years.

Methods
Operational method: The international unified intradermal injection standard was adopted. Specifically, 0.1 mL of tuberculin pure protein derivative (PPD, 5TU; Beijing Life Sciences Institute, Beijing, China) was slowly injected into the skin in the middle of the distal 1/3 area of the anterior side of the left forearm, using a 1-mL sterile disposable syringe with a No. 5 needle. Injection should be stopped until an orange peel-shaped, round skin elevation (Φ7–8 mm) had developed. Any overflow of the PPD solution should be avoided during the injecting process.

Recording method: Unified recording criterion of the PPD reaction: The average diameter of induration was recorded as follows: average diameter in mm=(horizontal diameter+vertical diameter)/2.

Judgment criteria: Negative reaction: A negative reaction was defined as no induration at the injection site or an average diameter of induration <5 mm. Ordinarily-positive: An ordinarily-positive reaction was defined as an average diameter of induration at the injection site of 5–9 mm. Moderately-positive: A moderately-positive reaction was defined as an average diameter of induration at the injection site of 10–19 mm. Strongly-positive: A strongly-positive reaction was defined as the average diameter of induration at the injection site was ≥20 mm, but with local bubbles, diabrosis, necrosis, or lymphagitis [4].

Chest X-ray examination, diagnosis, and diagnosis of exclusion: Patients with strongly-positive results received chest X-ray examinations. When abnormal shadows were detected in the lungs, the clinical symptoms were combined with further testing (sputum acid-fast staining, erythrocyte sedimentation rate [ESR], TB antibody titers) to substantiate the diagnosis or render a pre-diagnosis through consultation with an expert group. The clinical diagnosis of TB was according to the *Diagnosis and Treatment Guidelines of Pulmonary Tuberculosis* [5, 6], promulgated by the Chinese Society for Tuberculosis and Chinese Medical Association. Other TST-positive diseases and a history of TB were excluded before recommending prevention and treatment.

Grouping and chemoprophylactic protocol: One hundred seventy-nine patients with strongly-positive results, but without lung abnormalities or other diseases, were grouped using a digital random approach, as possible: 90 patients were in the prophylaxis group, the adults were administered 300 mg of isoniazid orally qd and children <12 years of age received 3–5 mg/kg qd (maximum dose=300 mg) for 10 months. The
patients in the control group did not receive any medications for the prevention and cure of TB.

**Signing the informed consent and follow-up evaluations:** Patients in the prophylaxis group were provided with teaching related to TB to inform them of the adverse drug reactions that might occur. After signing informed consent, the patients took medications for prevention under the guidance of TB specialist physicians and received regular follow-up evaluations of hepatic and renal function. The patients in the control group were informed of the clinical significance of strongly-positive TST results and the need to comply with follow-up visits. The patients in both groups were followed for 10 years and the TB morbidity rate was recorded. The number of patients with morbidity during different periods (<3 years, 4–7 years, 7–10 years, and ≤10 years) was compared. It was suggested that the TB patients be transferred to TB hospitals to receive standard anti-TB therapy.

**Computational formula of protection ratio:** The protection ratio was calculated as (the morbidity rate in the control group – the morbidity rate in the prophylaxis group)/(the morbidity rate in the control group×100%). Close contacts were defined as having dinner or living in the same room, or working and/or studying with TB-positive patients [7] for >6 months when the diagnosis of TB patients with positive results in sputum smear acid-fast bacilli were finalized.

**Statistical analysis:** SPSS19.5 statistical software was used for statistical analysis, and χ² was used to test data with a theoretical number <5. The corrected χ²-test was performed, and a \( P<0.05 \) indicated statistical significance.

**Results**

**TST results and the number of detected TB patients**
Among 1206 patients, there were 568 with negative results, 445 with ordinarily- and moderately-positive results, and 193 with strongly-positive results (positive rate=52.9% [638/1206] and a strongly-positive rate=16.0% [193/1206]). Fourteen TB patients were detected, all of whom had strongly-positive TST results (TB detection rate=1.1% [14/1206]).

**Prophylactic effect**

**Prophylactic effect within 3 years:** During the 3 years of follow-up visits, there were 4 patients in the prophylaxis group and 12 patients in the control group who acquired TB (morbidity rate=4.7% [4/84] and 13.4% [12/89], respectively; \( \chi^2=3.916, P=0.048 \)). The 3-year protection ratio was 64.6%.

**Prophylactic effect within 4–6 years:** During the 4–6 year period of follow-up visits, there were two patients in the prophylaxis group and three patients in the control group who acquired TB (morbidity rate=2.5% [2/78] and 4.1% [3/73], respectively; \( \chi^2=0.006, P=0.940 \)). Two patients in the prophylaxis group and four patients in the control group were lost to follow-up (lost to follow-up rate=2.5% [2/80] and 5.1% [4/77]; \( \chi^2=0.215, P=0.643 \)).

**Prophylactic effect within 7–10 years:** During the 7–10 year period of follow-up visits, there was one patient in the prophylaxis group and two patients in the control group who acquired TB (morbidity rate=1.3% [1/72] and 3.1% [2/64], respectively; \( \chi^2=0.011, P=0.918 \)). Four patients in the prophylaxis group and six patients in the control group were lost to follow-up (lost to follow-up rate=5.2% [4/76] and 8.5% [6/70], respectively; \( \chi^2=0.176, P=0.675 \)).

**Prophylactic effect at 10 years:** After 10 years of follow-up, there were 7 patients in the prophylaxis group and 17 patients in the control group who acquired TB (morbidity rate=8.3% [7/84] and 21.5% [17/79], respectively; \( \chi^2=4.770, P=0.029 \)). Six patients in the prophylaxis group and 10 patients in the control group were lost to follow-up (lost to follow-up rate=7.1% [6/84] and 11.2% [10/89], respectively; \( \chi^2=0.863, P=0.353 \)).

**Occurrence rate of adverse drug reactions:** Six patients in the prophylaxis group discontinued isoniazid midway during the study due to adverse drug reactions. The occurrence rate of adverse drug reactions was 6.6% and the medication completion rate was 93.3%.

**Discussion**
Tuberculosis is mainly transmitted through droplet contact, and contact within a close distance increases the
probability of infection. One survey involving close contacts with smear-positive TB patients in the US indicated an infection rate of 20%–30% [8]. A domestic survey on medical staff in TB-designated medical institutions showed that the risk of infection with TB for medical staff was 2.581-fold [9] non-designated medical institutions. Another survey was conducted on an ordinary group, and showed the latent TB infection rate of close contacts with smear-positive TB patients was 48.7%, with a detection rate of active TB of 1.9% [10]. In a retrospective investigation involving pediatric patients with TB, it was shown that 85% of patients had a definite or possible TB contact history [11]. Zhu reported that one-third of pediatric patients with TB had a definite contact history, and two-thirds had a history of BCG inoculation [12], which illustrated that intimate contact is a high-risk factor for TB and should thus be a focus of attention.

Following infection with *M. tuberculosis*, 5%–10% of those infected develop active TB, and in most cases active TB develops within 2 years of infection [13]. Latent TB infection (LTBI) develops in 90% of those infected with an absence of clinical symptoms. Among patients with LTBI, 10%–20% have active TB when protective immunity is impaired, and 80%–90% are not pathogenic [14]. The results of a study involving close contacts showed a positive rate of 36.9%, a strongly-positive rate of 16.0%, and a TB detection rate of 1.1%. Isoniazid was adopted for prevention and cure. At the time of the 3-year follow-up visit, the morbidity rate of the prophylaxis and control groups was 4.7% and 13.4%, respectively; however, there was no difference in morbidity between the 4–6 and 7–10 year follow-up periods. By 10 years of follow-up, the total morbidity of the prophylaxis and control groups was 8.3% and 21.5%, respectively. Isoniazid clearly had a prophylactic effect within the first 2–3 years of treatment. Although adverse drug reactions occurred during the period medication was prescribed, most of the affected patients were children. It is possible that children were affected more often than adults because children are in the growth and development period and sensitive to drug reactions with abnormal liver function, while adults had no adverse drug reactions. Thus, isoniazid prevention is safe for adults.

The PPD skin test is an important clinical method of detection to screen for *M. tuberculosis* infection, but the PPD skin test is influenced by BCG inoculation, especially in children. Although the γ-interferon release test [15], which is based on T cell mediated cell-mediated immunity [16], has a higher sensitivity and specificity than the TST, the difference between the two methods of detection is not statistically significant [17]. In addition, the γ-interferon release test has a high cost and the technique is tedious; therefore, the TST is still widely used in clinical diagnosis and differential diagnosis of *M. tuberculosis*.

Drug prophylaxis is mainly used to cure active TB that develops from the type with a comparatively high risk. The latent-infected patients benefiting from the corresponding therapy were divided into two categories (patients with a high risk of infection, including close contacts and patients from high epidemic areas, and patients with a high risk of morbidity after infection, such as HIV-infected patients, recent TST conversions, and children ≤5 years of age [18]. Following infection with *M. tuberculosis*, the pathogen can survive in the human body for a long time, and 10% of infected patients develop active TB [19]. Isoniazid is the earliest and most commonly used drug for TB prevention, so studies on isoniazid prevention are relatively mature. In the mid-1950s, there were >20 studies on the application of isoniazid in the prevention and cure of latent infections, and the study results showed that the TB cases was reduced by approximately 60%. The after-treatment effect could reach 90% [20]. Isoniazid can prevent TB over the long-term, and in the event of no infection from the outside world, the prophylactic effect might be lifelong [21]. The course of prevention of isoniazid is 6–12 months. The current study adopted a prevention protocol lasting 10 months, and the patients were followed for 10 years. In the current study, the morbidity rate of the prophylaxis group was less than the control group, with an occurrence rate of adverse drug reactions of 6.6%, and the medication completion rate of 93.3%. Within the first 2–3 years after treatment, there was a difference in morbidity, and with time there was no difference in the morbidity rate. After infection of humans with *M. tuberculosis*, the actively metabolized bacteria might be killed by isoniazid or eliminated by immune cells. The bacteria that were not killed were sequestered or became dormant, and subsequently became a source of relapse. The course of prevention of a single drug is comparatively long and compliance is favorable. In recent years, a new short prevention and cure protocol has been
developed; specifically, rifampin or rifapentine in combination with isoniazid for 4 months, but the occurrence rate of adverse drug reactions is high [22]. Within a course of treatment of 6–12 months, the occurrence rate of adverse drug reactions of isoniazid monotherapy is 1.3%–11.3% [23]. Treatment of LTBI is classified as preventive treatment, and attention should be paid to safety. The issues that should be considered are the selection of proper therapeutic regimens and evaluation of the risk of adverse drug reactions. In addition, TB should be excluded to avoid generation of drug resistance. Before administration of preventive drugs, risk factors (alcohol addiction, chronic liver disease, and HIV infection) for liver damage should be evaluated and the baseline value of aminopherase should be determined [24]. During treatment, liver function tests need to be tested as per requirements.

Tuberculosis invariably ranks first place among legally-reported epidemic diseases. TB is a severe domestic issue that should include prevention and cure. The previous treatment strategy placed particular stress on diagnosis, treatment, and isolation of patients, but with technologic improvement and a change in awareness of TB treatment, prevention and cure will exert their effects gradually. Preventive drugs will be frequently adopted by high-risk patients to reduce the morbidity rate of TB over the long-term. The polymorphic site, rs7194886, of the immunity-related gene, NOD2, might be correlated with the genetic predisposition to TB in a Chinese population [25]. Hence, it is necessary to continue to study more accurate examination methods, as well as diagnosis and prevention methods, to optimize preventive treatment and reduce excessive therapy.

Conflict of interest
The authors declare no conflict of interest.

References