Comparison of Sensitivities to Two Commercially Available Tuberculin Skin Test Reagents in Persons with Recent Tuberculosis

J. S. Duchin, J. A. Jereb, C. M. Nolan, P. Smith, and I. M. Onorato

Discrepancies have been reported between results obtained with tuberculin skin tests (TSTs) performed with use of different reagents. We compared TST results and determined the sensitivities of the two commercially available TSTs in 51 human immunodeficiency virus–negative persons with culture-confirmed active tuberculosis. Simultaneous TSTs were done with use of the Mantoux method and 5–tuberculin unit purified protein derivative (PPD) tuberculin preparations from single lots of Aplisol and Tubersol. Aplisol skin test reactions ranged from 5 mm to 26 mm (median, 16.0 mm), and Tubersol reactions ranged from 7 mm to 23 mm (median, 15.0 mm). The mean difference in paired reaction sizes for the two reagents was 0.58 mm and was not statistically different from zero (P value, 0.26). The difference in reaction sizes was ≤2 mm in 55% and ≥5 mm in 18% of patients. With a cutoff of either 5 mm or 10 mm to define a positive reaction, all results were concordant, with sensitivity of 100% and 96%, respectively. We found indistinguishable reaction size distributions and median TST results for the two commercially available PPD TST reagents, Aplisol and Tubersol, in a population with recent culture-proven tuberculosis.

It is estimated that 10–15 million persons in the United States are infected with Mycobacterium tuberculosis [1]. Accurate detection of infection, especially in persons at highest risk for progression to clinical disease, is necessary for prevention of disease. The tuberculin skin test (TST) employing intradermal injection of 5 TU of PPD tuberculin (Mantoux test) is currently the preferred technique for detecting asymptomatic, latent M. tuberculosis infection [2]. Falsely positive results from tuberculin skin testing may lead to unnecessary evaluation and treatment of uninfected persons and unwarranted epidemiological investigations. However, the specificity of the TST varies according to the prevalence of exposure to nontuberculous mycobacteria [3], and reports of unexpected or falsely positive TST results as well as discrepancies between results obtained with available TST reagents raise important questions about the standardization and performance characteristics of the two PPD reagents commercially available in the United States, Aplisol (Parke-Davis, Morris Plains, NJ) and Tubersol (Connaught, Swiftwater, PA) [4–9].

See editorial response by Sbarbaro and Iseman on pages 644–5.

The findings of a 1982 investigation comparing two lots of Aplisol and a single lot of Tubersol suggested that false-positive TST results were associated with a single lot of Aplisol [10]. Also in 1982, a multicenter study found significantly greater mean reaction sizes with Aplisol than with Tubersol and PPD-standard (PPD-S) [11]. In that same year, production and distribution of Aplisol from the old master batch of tuberculin was stopped and a new master batch was prepared [11]. Because the sensitivity of tuberculin testing with these reagents has not been compared recently, we compared the reaction distributions of single lots of the two commercially available PPD TST reagents in the United States, Aplisol and Tubersol, when simultaneously administered to persons with previously culture-proven tuberculosis.

Methods

Persons aged 18 years and older were recruited from the Seattle–King County (Washington) Department of Public Health Tuberculosis Clinic. Eligibility criteria were (1) either the occurrence within the past 5 years of culture-confirmed tuberculosis that resolved with treatment or else current culture-confirmed tuberculosis for which at least 2 months of antituberculosis therapy had been received and had reduced the signs and symptoms of disease; (2) a negative HIV test by ELISA at study enrollment (49 patients) or within the previous 2 years (two patients); and (3) no prior adverse reaction to tuberculin skin testing (including blistering, ulceration, or scarring).
A sample-size calculation showed that for detection of a mean difference in reaction size of ≥2 mm, with alpha = 0.05 and beta = 0.85 (power = 85%), the required sample size was 34 paired results, achieved with 17 subjects undergoing two tests each.

The study protocol was approved by the Human Subjects Review Committee of the University of Washington and the Centers for Disease Control and Prevention. After informed consent was given, subjects underwent simultaneous TSTs using the Mantoux method and 5-TU PPD tuberculin preparations from single lots of Aplisol (lot number 02804P) and Tubersol (lot number 2403-11) provided by the manufacturers. The tests were administered and read in a double-blind design.

Prior to placement of the TST, each reagent was randomly assigned to the subject’s volar surface of the right or left arm and loaded into coded tuberculin syringes labeled only “right” or “left” by an investigator not performing the skin testing. Skin testing was performed by a single nurse experienced in placing tuberculin skin tests and measuring the reactions. Subjects returned in 48–72 hours, and results of each test were recorded in millimeters of induration; any adverse events also were recorded. The reagent code was broken upon completion of the study.

Clinical information was collected through medical record reviews with use of standardized abstraction forms and included demographic data, organ site of tuberculosis disease, date and source of specimen positive for M. tuberculosis, history of antituberculosis treatment, current medications, and medical conditions known to decrease reactivity to tuberculin.

The mean difference in induration for the reagents was compared with the Student’s paired t-test and a two-tailed significance level of 5%. We chose 5-mm and 10-mm cutoffs to calculate sensitivity because these values are currently recommended for determining TST positivity in populations at increased risk for tuberculosis infection [2].

Results

Fifty-one persons with active tuberculosis diagnosed between December 1992 and March 1995 were enrolled in the study. The median age was 41 years (range, 21–85 years); 35 (69%) of the patients were male, 25 (50%) were Asian or Pacific Islanders, 16 (32%) were white, 7 (14%) were black, and 2 (4%) were Native American (race was unspecified for 1 patient). Thirty subjects had immigrated to the United States; 22 (73%) were from Southeast Asia and the Philippines, and 21 (70%) had immigrated within the past 5 years.

M. tuberculosis was cultured from a pulmonary source in 44 (86%) of the cases. The remaining sites yielding positive cultures included bone in two cases and lymph node, peritoneal tissue, CSF, and rectal biopsy specimens in one case each. All subjects tested negative for HIV-1 by ELISA at enrollment, and none was taking immunosuppressive medications or had medical conditions that cause immunosuppression. The PPD skin tests were read at 48 hours for 45 patients (88%) and at 72 hours for six (12%).

The reaction-size distributions for the two reagents are depicted in figure 1. Aplisol skin test reactions ranged from 5 mm to 26 mm (mean, 15.6 mm; median, 16.0 mm), and Tubersol reactions ranged from 7 mm to 23 mm (mean, 15.0 mm; median, 15.0 mm). There were no significant differences in the mean reaction size by age, race, gender, site of disease, or time from diagnosis of tuberculosis. The paired differences in Aplisol minus Tubersol reaction sizes for each subject are depicted in figure 2. The mean difference in paired reaction sizes for the two reagents was 0.58 mm (range, 0–11 mm) and was not statistically different from zero (P value, 0.26). The difference in reaction sizes was ≤2 mm in 55% and ≥5 mm in 18% of patients. With a cutoff of either 5 mm or 10 mm to define a positive reaction, all results were concordant. No subject experienced blistering related to tuberculin skin testing.

Discussion

Several recent reports highlight the uncertainty surrounding the interpretation of TST results in clinical situations, especially when positive results are unexpected. Lifson et al. [6] reported that among 42 intravenous drug users undergoing TST screening and with an initial reaction to Aplisol of ≥5 mm, 11 (26%) had no reaction upon retesting with Tubersol (5 of 9 HIV-positive and 6 of 33 HIV-negative persons). Rupp et al. [4] reported that among 26 employees found to have a positive TST after initial screening with Aplisol, only four had a positive result when retested with Tubersol. Cieslak et al. [5] reported a cluster of false-positive TST conversions in 11 pediatric patients initially tested with Sclavo (Sclavo, Wayne, NJ) who retested negative with Aplisol (all Sclavo lots were subsequently recalled by the manufacturer).

![Figure 1. Tuberculin skin test reaction sizes in patients tested with Aplisol and Tubersol reagents.](https://academic.oup.com/cid/article-abstract/25/3/661/291372)
In contrast, we found indistinguishable reaction-size distributions and median TST results for the two commercially available PPD TST reagents, Aplisol and Tubersol, when applied simultaneously in a population with recently culture-proven tuberculosis. Both reagents showed a unimodal distribution of reaction sizes centering around 15–16 mm, consistent with previous reports of TST results in populations with M. tuberculosis infection [12]. Chaparas et al. [13] tested 91 patients with confirmed tuberculosis with two injections of PPD-S tuberculin to examine variability with the Mantoux test using the same reagent. TST results were reported in categories of 0 mm, 1–4 mm, 5–9 mm, 10–14 mm, and >15 mm and showed 86% and 87% agreement when read at 48 and 72 hours, respectively.

In the Chaparas study 13% of subjects had a one-category disagreement in TST results. Using two different reagents, we found 18% of subjects to have a >5-mm difference between the two reagents tested. Although not directly comparable because of differences in study design, our results are consistent with those reported when the identical TST reagent was used in two arms of the same subject and may represent variability inherent in tuberculin testing [13–15]. Most noteworthy in the current study is that all readings were concordant, with sensitivity of 100% and 96%, respectively, at cutoffs for positivity of 5 mm (all subjects above cutoff) and 10 mm (49 of 51 subjects above cutoff).

Although the generalizability of our findings is limited, we found no significant differences in the reaction profiles for the lots of Aplisol and Tubersol we tested. It is possible, however, that the performance characteristics of different lots of PPD tuberculin may vary [10]. Previous reports of discrepancies in TST reactions for Aplisol and Tubersol have been concerned with false-positive reactions (specificity). Because we evaluated the PPD reagents in persons with recently proven tuberculosis, the results do not allow us to determine the specificity of the tests. Additional studies are needed to evaluate the specificity of TSTs in populations at low risk of tuberculosis infection, specifically health care workers, for whom the consequences of false-positive results are of greatest impact with regard to individuals and the public health.

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References