Selected Summaries

Tuberculin Test

[Pouchot], Grasland A, Collet C, Coste }, Esdaile } M, Vinceneux P. Reliability of Tuberculin skin test measurement. Ann Intern Med 1997; 126: 210-214].

Correct measurement of tuberculin skin test is vital and errors are likely to influence the decisions to commence antituberculous therapy. Standardization of the tuberculin reagent and the meaning of the test results are often widely discussed but scant attention has been given to the induration itself.

A cross sectional study was conducted in a University hospital in France to determine the reliability of tuberculin skin testing and to compare the customary technique of palpation of the size of induration with the alternative ballpoint-pen method. Purified protein derivative tuberculin (5IU) was given intradermally on the volar surface of the forearm (Mantoux technique) to 96 people who were either patients or health care personnel in an internal medicine department who had received BCG vaccine previously. Readings were recorded on the third day by two experienced investigators who independently did three measurements. The first two measurements were taken with a blinded caliper using the ballpoint-pen technique. With this technique, a medium point ballpoint pen was used to draw a line starting 1 to 2 cm away from the skin reaction along the long axis of the forearm and moving towards its center. When the pen reached the margin of the induration, an increased resistance to further movement was felt and the pen was lifted. The procedure was repeated on the opposite side of the skin reaction. The distance between the ends of the opposing lines at the margins of the induration was measured. The lines were erased and the measurement process was repeated. The lines were again erased and the third measurement was done by palpation. To reduce the chances of error, results of measures that were obtained with the blinded caliper, were recorded by a third investigator.

Global intra and interobserver reliability coefficients of the ballpoint pen technique were high. Five per cent of the time, however a second measurement by the same observer could be atleast 2.7 mm less to 3.0 mm more than the first measurement and the measurement from the second observer could be atleast 3.4 mm less to 3.7 mm more than the measurement from the first observer. This could lead to the reclassification of a positive test results as negative or vice versa. The area of imprecision was 38% less broad for the ball point-pen technique than the palpation method.

[Oztwik P, Eskiocak M, Bay A, Sancak R, Dabak S, Gnrses N. Predictive value of a 24 hour tuberculin skin test evaluation. Arch Dfs *Child 1997; 76: 452-453].*

The tuberculin skin test is used to detect local hypersensitivity to *M. tuberculosis.* According to current recommendations only indurations read at 48 to 72 hours are valid. A study was undertaken to determine the value of the induration 24 hours after intradermal injection of the purified protein derivative in children.

A total of 1082 school children (ages 6-17 years) in Turkey were recruited in the study. The children had not been given BCG or tuberculin skin test in the previous

five years, and none had a condition known to cause anergy. Twenty four hours after intradermal injection of 5 tuberculin units of PPD, the maximum transverse diameter of induration was measured with a transparent plastic ruler by two of the authors, by palpation technique. At 48 and 72 hours, second and third measurements were done by the same readers. The readers were blinded during all the three readings. Sensitivity, specificity and predictive values were calculated for the indurations at 24 hours. There were no differences between the reader's ability to measure the size of the induration independently ($p > 0.05$). The mean (SD) size of the induration at 24 hours was less than that of the induration present at 48 and 72 hours. Differences were statistically significant ($p < 0.001$). There was no difference between 48 and 72 hours reading ($p > 0.5$). Any induration 24 hours after placement of the tuberculin test had a sensitivity of 94% and' a specificity of 75%. At 24 hours, induration of any size had a relatively low positive predictive value (63%), although induration > 5 mm had a higher (86%) positive predictive value.

Comments

Infection with *M. tuberculosis* sensitizes the person to the antigenic components contained in tuberculin. The Mantoux reaction, obtained by injecting tuberculin intradermally elicits a delayed hypersensitivity reaction with induration and erythema which peaks at 48 to 72 hours and subsides over a period of 5-6 days. The test is read by measuring the size of induration at 48 to 72 hours when the hypersenstivity reaction is maximal(l). The size of the induration can be measured by palpation method or ballpoint-pen technique. It is customary to measure size of the induration by palpation. The alternative ballpoint-pen technique which delineates the margins of the induration more clearly and is therefore more accurate, has not been discussed in relevant official statements on tuberculosis(2,3). Studies demonstrating the better accuracy of ballpoint technique are scant(4). The current study found the ballpoint pen method more reliable as evaluated by global reliability coefficients. In addition to the method employed to measure the size of induration, there are significant differences in the sizes of reactions recorded by experienced and inexperienced readers. The intra observer and interobserver reliability has been evaluated in a few previous studies(5,6). Results from these studies are conflicting as none of these used reliability coefficients, which is the recommended method. Most of these studies were restricted to the palpation method and only one study described the inter-observer reliability of the ballpoint pen technique(7). In the present study ballpoint pen technique demonstrated high intra and interobserver reliability coefficients. However, in 5% of the cases reading of tuberculin skin tests resulted in erroneus values especially when measurements were close to the cut off point that separates negative from positive results. Thus the sources error in measuring the size of induration of tuberculin test could be minimized by using the ballpoint pen method and improving intra-observer reliability by taking average of two consecutive measures taken with a blinded gauge.

The second study evaluated the predictive value of a 24 hour tuberculin skin test. An early study by Howard and Solomon in adults showed that size of induration at 24 hours was highly predictive of eventual findings at 48 to 72 hours(l). In children the positive predictive value of any induration (> 1mm) reading at 24 hours was relatively low (63%) when a cut off of > 10 mm was

used, but increased to 86% if the size of induration was > 5 mm at 24 hours. The present study demonstrated that it will not always be possible to tell whether any induration (> 5 mm) will develop into a positive test but if there is no induration especially in children younger than 13 years, it is highly possible (98%) that the tuberculin test will be negative.

In conclusion, a physician must keep in mind the potential sources of errors in recording the size of induration of a tuberculin test. Most of these errors can be avoided by careful attention.

K. Rajeshwari,
Department of Pediatrics,
Hindu Rao Hospital,
Delhi 110 007.

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Routine Antipyretic Therapy in Malaria?

[Brandts CH, Ndjave M, Graninger W, Kremsner PG. Effect of paracetamol on parasite clearance time in Plasmodium falciparun malaria. Lancet 1997; 350: 704-709].

Routine antipyretic therapy in children with infectious diseases including malaria is a common practice. However, the utility of this practice is contraversial and is yet to be scientifically substantiated. A randomized trial was conducted in Lambrene, Gabon to assess the effect of paracetamol on parasite clearance time in *P. falciparum* malaria. Fifty children with uncomplicated P. *falciparum* malaria who were febrile on admission or had fever in the past 24 hours but had not received any antimalarials were enrolled in the study. They were admitted and treated with inravenous quinine and were randomized to receive either mechanical antipyresis alone (n=25) or in combination with paracetamol (n=25). Mechanical antipyresis was achieved by continuous electric fanning and tepid sponging and cool blankets were used if temperatures rose to > 37.5° C. Paracetamol was given in a dose of 10-15 mg/kg every 6 hours which was shortened to 4 hours

duration if fever rose to > 37.5° C. Rectal body temperature was measured every 6 hours for 96 hours and parasitemia was assessed by a Giemsa stained thick blood film every 6 hours till parasites were cleared for 24 hours. Tumor necrosis factor (TNF), interleukin-6 (IL-6) and oxygen radical concentration were measured in daily plasma samples and also after stimulation with phytohaemagglutinin.

Of the 50 children enrolled, 47 completed the trial. Fever clearance time (FCT), *i.e.,* time till the temperature remained below 37.5° C for 24 hours was found to be 32 hours in children treated with paracetamol, compared with 43 hours in children who received mechanical antipyresis alone. However, this 11 hours difference was not statistically significant (p = 0.176). Parasite clearance time (PCT) was significantly prolonged in patients who received paracetamol (75 hours *vs* 59 hours p = 0.004).

Plasma concentration of TNF and IL-6 were similar in both groups. However, the induced concentration of TNF and production of oxygen radicals were significantly lower in children treated with paracetamol. It was thus concluded that paracetamol has no antipyretic benefit over mechanical antipyresis in *P. falciparnni* malaria. However, it prolongs parasite clearance time possibly by decreased production of TNF and oxygen radicals.

Comments

Controversy persists over the use of antipyretic drugs in malaria. Pharmacological antipyresis has been advocated to reduce the risk of febrile convulsions and alleviate the feeling of ill health associated with fever through their analgesic effect. However, data(l) indicates that seizures can occur in malaria at temperatures below 38° C in a majority of patients, thus suggesting alternate pathogenesis of these seizures.

The present study has shown that paracetamol has no added benefit over mechanical antipyresis on the outcome of fever. This is in contrast to a previous study in adults(2) which had shown a mean reduction of temperature by 2.1° C with paracetamol in addition to quinine in comparison to quinine alone. This study also questioned the conventional antipyretic effect of quinine.

Another adult study proved that ibuprofen was significantly more effective than paracetamol in lowering temperatures throughout the first 4.5 hours after a single dose (p = 0.016) in patients with P. *falciparum* malaria(3). This temperature response was also mirrored in the symptomatic improvement reported by the patient.

TNF is an important mediator of malarial fever and previous studies(4) have shown that TNF acts to suppress the parasite, but may also contribute to the pathogoenesis of fatal malaria. Mean plasma TNF levels, have been found to be 10 times higher in fatal cerebral malaria than in uncomplicated malaria(5). Patients with high plasma concentration of TNF and IL-6 produce small amount of either substance in response to phytohaemagglutinin stimulation. However, high inducable TNF levels predict a shorter parasite clearance time which has been validated in the present study also. This study also showed that paracetamol reduced inducible TNF levels on day 1 of the study which probably resulted in delayed parasite clearance. It was postulated that this was a direct effect of paracetamol rather than due to fever reduction. The antiparasitic action of TNF may be due to production of oxygen radicals. Paracetamol treated children had significantly lower production of oxygen free

radicals after 4 days of treatment which suggests that delayed parasite clearance action of paracetamol may act by decreased inducible TNF leading to low oxygen radical concentration.

It may be concluded that further studies will be needed to establish the deleterious effect of paracetamol on parasite clearance in malaria before specific recommendations on the same are made. The over riding priority in the management of severe malaria is to save life, whereas symptomatic relief is one of the objectives in the management of uncomplicated malaria. Thus the beneficial effect of analgesics including paracetamol in alleviating patient discomfort should not be underrated.

Shaguna C. Mahajan,
Senior Resident,
Department of Pediatrics,
Manlana Azad Medical College,
New Delhi 110 002.

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