Editorial

RATIONALE FOR CHEMOTHERAPY OF TUBERCULOSIS AND CURRENT RECOMMENDATIONS

Short course (SC) chemotherapy of tuberculosis is now accepted treatment for most forms of tuberculosis. The availability of rifampicin (RIF) and pyrazinamide (PZA) made the intensive phase (initial 2-month period) of the 6 months SC Chemotherapy regimens possible. The intensive phase of the therapy consists of INH, RIF and PZA [and Streptomycin (STM) or ethambutol (ETB), if indicated] followed by 4 months of INH and RIF(1-4). The many advantages of SC therapy are better compliance, achieving faster sterilization, lower treatment failures and relapse rates due to broader coverage to tackle possible drug resistant mycobacteria. In addition, these regimens are cheaper and patients are exposed to potentially toxic drugs for a shorter duration(1).

The SC chemotherapy regimens were first tried and tested in adults although peculiarities of childhood tuberculosis make it more amenable to SC regimens. These include lack of cavitary lesions in primary pulmonary tuberculosis and higher rate of occurrence of extrapulmonary tuberculosis, both associated with lower bacillary load. In addition, there is less secondary bacterial resistance. Children tolerate higher drug dosage and have lower incidence of adverse reactions(1,2).

Trials of SC chemotherapy in childhood tuberculosis except for CNS tuberculosis have been done in many countries. A review of these trials shows that SC chemotherapy is very effective(1,2). A trial conducted in India has been considered amongst the best controlled studies(5).

It is important to understand the basis of SC therapy. The size of the bacillary population is the main biological determinant of the anti-tuberculosis therapy. Thus, in children with infection (significant positive skin test) but no disease, the bacterial population is very small (10^3–10^4 organisms) and drug resistant mutants are low so that a single drug INH can be used(1-3). Primary pulmonary and extrapulmonary tuberculosis have medium sized bacillary populations and drug resistant mutants may or may not be present. Mutants naturally resistant to two drugs are almost nonexistent. As bacterial population is smaller in children, the chances of having drug resistant bacilli are reduced proportionately(1-3).

A hypothesis has developed due to several biologic characteristics of *M. tuberculosis* regarding action of drugs. *Mycobacteria* live in the host as different cell populations, from inactive or dormant forms to metabolically active, replicating forms. They replicate best where oxygen tension is high, and pH neutral or alkaline; optimal conditions are present in the tuberculous cavities. Thus bacterial populations are large in cavities for which INH, RIF and STM are the most effective drugs. In closed caseous lesions where activity of *M. tuberculosis* is slow and intermittent, RIF and INH are more useful. Pyrazinamide, RIF and INH are effective

against the intracellular mycobacteria which are the least active. The extent of bactericidal and sterilizing activity and prevention of resistance varies for different antitubercular drugs. The highest bactericidal activity is attributed to INH. It contributes maximally to prevention of resistance whereas RIF has highest sterilizing activity(1,3). Though there is only a small chance of children harbouring drug resistant tubercle bacilli, drug resistance should be considered in a child who has been earlier treated for tuberculosis or whose adult contact received antituberculosis treatment(1-4). In such situations, STM or ETB should be added. The World Health Organization (WHO)(4), the International Union of Tuberculosis and Chest Disease (INUTCD)(2) and the American Academy of Pediatrics (AAP)(3) and others(1) have made recommendations regarding the SC chemotherapy regimens in children. The drug dosages advised by WHO(4) and IUTCD(2) are similar while those by AAP(3) for INH and RIF are somewhat higher and shown in parenthesis. For daily drug regimens, INH 5 (10-15) mg/kg, RIF 10 (10-20) mg/kg and PZA 35 (20-40) mg/kg is recommended. Dose of ETB is 25 (15-20) mg/kg and that of STM 15-20 (20-40) mg/kg body weight. For intermittent regimens, INH 15 (20-40) mg/kg, RIF 10-15 (10-20) mg/kg and PZA 50 (50-70) mg/kg is recommended. As regards ETB, a dosage of 30 mg/kg (thrice a week) or 45 mg/kg (50 mg/kg) twice a week is advised. Steptromycin is to be given 15-20 (20-40) mg/kg twice a week(2-4).

Pharmacokinetic studies of INH in children have shown that plasma and serum levels are 50-100 times the MIC when the former dose is used orally. CSF levels are only slightly lower (90% of serum levels), even when meninges are not inflamed. Hepatotoxicity is uncommon but increases with increase in dosage and concurrent use of RIF(2).

As rates of adverse reactions are low, no routine monitoring of hemogram, liver function tests and uric acid estimation are required(1) but patient must maintain frequent contact with treating doctor or trained paramedical staff.

Young children less than 4 years of age are at high risk of developing hematogenous spread (meningeal and miliary). Therefore, drugs like INH, RIF and PZA which diffuse readily into CSF must be included in all SC regimens(1).

Intermittent SC chemotherapy drug regimens should be supervised. This supervision can be provided by hospitals or at primary health care levels by paramedical staff or even by a responsible community or family member(1-4).

Although enough data regarding SC therapy is not available in tuberculous meningitis (TBM) and bone and joint tuberculosis there is no good reason to believe that this form of therapy will be less efficacious. Studies done on TBM suggests that SC therapy may be possible in TBM(6). Until further information, one year therapy is recommended.

Children with human immunodeficiency virus (HIV) infection with tuberculosis should receive at least 3 drugs but therapy should be continued for longer time–9 months (based on data from adults)(3). Culture confirmation and drug susceptibility patterns should be obtained(3,4) as atypical mycobacteria are likely to cause the disease.

Corticosteroids can be used in tuberculous meningitis, pleural and pericardial effusions, miliary and endobronchial tuberculosis in initial 4-6 weeks of therapy(3).

As regards prevention, tuberculin

negative children with known contact should receive INH 5 mg/kg/day (not to exceed 300 mg) for 12 weeks after the contact has been broken and Mantoux test given. If positive, INH should be given for 6 months. Those who are tuberculin positive with known contact should receive INH in above mentioned dosage for 6 months to prevent development of serious forms of disease. Those known to be newly infected (tuberculin conversion within past 2 yeas) if under 6 years of age should also receive INH(2). RIF can be given if the strain is INH resistant(3).

Some of the pediatric formulations may not be appropriate. Addition of RIF in a cosuspension or multi-suspension leads to marked reduction in concentration of one or more drugs. Addition of Vitamin C accentuates the problem(7). Based on this information it is recommended that cosuspensions or multi-suspensions containing RIF or Vitamin C should not be dispensed.

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