Editorial

SHORT COURSE CHEMO-THERAPY IN CHILDHOOD TUBERCULOSIS

The era of modern anti-tubercular chemotherapy began in 1952. The discovery of newer, more potent antitubercular drugs revolutionized chemotherapy for tuberculosis making it a truly curable and preventable disease. Significant advances in the treatment of tuberculosis have occurred with the introduction of short course chemotherapy in early 1980's. It has superior sterilizing and bactericidal action, shorter duration, lower failure and relapse rates, broader coverage for possible drug resistant *Mycobacterium tuberculosis* and is cost effective.

The currently recommended regimen for pulmonary and most forms of extra-pulmonary tuberculosis in children is 6 months of isoniazid and rifamipicin supplemented during the first 2 months by pyrazinamide. The addition of pyrazinamide to the initial phase of therapy permits shortening of the total duration of treatment to 6 months for most patients(1-3). Ethambutol or streptomycin should be added to this regimen for any patient with an increased chance of having resistant disease, tuberculous meningitis or disseminated tuberculosis. Treatment during the first 1-2 months should if possible, be daily but the last 4-5 months of therapy can be daily or twice or thrice weekly under direct observation of a health care professional. If social or other constraints prevent regular self administration in the initial phase, medication may be administered twice daily from the beginning under close observation. Under these circumstances a total duration of treatment of 6 to 9 months is reasonable. Nine months of treatment with isoniazid and rifampicin administered daily for 2 months and followed by isoniazid and rifampicin given daily or 2 to 3 times a week, is also effective and safe(4).

In tuberculous meningitis the relative lack of data at present leads most experts to recommend the total duration of therapy between 6-12 months. Intensive 'short course chemotherapy (6 months) with pyrazinamide is more efficacious than longer courses (9 or 12 months) without pyrazinamide in preventing total negative outcome and sequelae(l,2).

Tuberculous lymphadenitis in children has been successfully treated with fully supervised intermittent chemotherapy regimen consisting of streptomycin, rifampicin, isoniazid and pyrazinamide three times a week for two months followed by streptomycin and isoniazid twice a week for four months on an outpatient basis, with 5% relapse on a follow up of three years(5). Short term chemotherapy was used in tuberculosis of the spine, (thoracic or lumbar) for 6 months and resulted in good resolutions(6).

The global tuberculosis epidemic is being fuelled by dual infections with human immuno deficiency virus and M. *tuberculosis.* The response to anti-tuberculosis drugs in HIV positive individuals has been excellent provided the strains were susceptible and compliance was maintained. Short course chemotherapy is effective but usually fails due to operational reasons. Fully supervised therapy has high compliance(7).

The dose of anti-tuberculosis drugs recommended by International Union Against Tuberculosis (1991) are isoniazid-5 mg/kg/day (maximum 300 mg), rifampicin 10 mg/kg/day (maximum 600 mg), pyrazinamide 35 mg/kg/day (maximum 2 g), streptomycin 15-20 mg/kg/day,and ethambutol 25 mg/kg/day for 2 months followed by 15 mg/kg/day thereafter;

For intermittent use, the dose of isoniazed and rifampicin are 15 mg/kg, streptomycin 15-20 mg/kg, pyrazinamide 50 mg/kg thrice a week or 75 mg/kg twice a week, and ethambutol 30 mg/kg thrice a week or 45 mg/kg twice a week(8).

The adverse effects of these drugs are uncommon in children and are dose related. Hepatitis occurs in less than 1% of children receiving both isoniazid and rifampicin. It is more frequent in slow acetylators than in rapid acetylators. Pyrazinamide does not contribute to the hepatotoxicity. Treatment is interrupted if the serum transaminase levels exceed 3-5 fold the normal values. Ethambutol causes retrobulbar neuritis, which is reversible if the drug is withdrawn in the early stages of adverse effects. It should not be given to children if visual acuity and color vision cannot be tested.

The biggest hurdle in the short course chemotherapy is non-compliance which leads to treatment failure, acquired drug resistance, death and disability. Therapy should, therefore, ideally be monitored.

The bacteriological basis for current chemotherapy is based on the following characteristics of *M. tuberculosis: (a)* there is a high rate of mutation with resistance to anti-tubercular drugs. A wild strain of *M. tuberculosis* will have one out of every 10^5 to 10^8 bacilli resistant to any single anti-tubercular drug. Dual resistance to isoniazid and rifampicin is rare; and (b) in unfavorable conditions *M. tuberculosis* will grow only intermittently or remain dormant for a prolonged period. Hence there is a need for prolonged treatment to prevent relapse and multidrug regimen to prevent the emergence of resistant organisms.

In human disease, it is postulated that M. *tuberculosis* organisms exist in several subpopulations, each of which has a distinctive metabolic status and varying vulnerability to antitubercular drugs. The bacillary load in the wall of the cavitary lesions is high as the conditions for growth are favorable because of high oxygen content and a neutral pH. This subpopulation is particularly vulnerable to isoniazid and to a lesser extent to rifampicin, streptomycin and ethambutol.

A second subpopulation exists intracellularly in an acidic environment. Pyrazinamide is active in an acidic medium and is effective in this subpopulation. Isoniazid, rifampicin and ethambutol are less active(9).

The third subpopulation is localized

mainly in caseous material where the pH is neutral but the oxygenation is poor. Organisms grow very slowly with occasional spurts of active metabolism. This group is killed by rifampicin because its bactericidal action starts very quickly.

A fourth subpopulation is completely dormant and antitubercular drugs have no action against it. There may be a constant shifting between these populations.

Based on clinical trials and animal experiments, there are three categories of antitubercular drugs. Bactericidal drugs have the ability to kill large numbers of actively metabolizing bacilli rapidly. Isoniazid is the most potent bactericidal drug and it is estimated that it may kill 90% of the bacillary population during the first few days of chemotherapy. Rifampicin is also an important bactericidal drug. Streptomycin, pyrazinamide and ethambutol are less potent drugs.

Rifampicin and pyrazinamide are the most important sterilizing drugs because of their ability to kill semidormant bacilli. Such bacilli are capable of surviving the bactericidal action of isoniazid and of giving rise to relapse after treatment.

Populations of tubercular bacilli which have not been exposed to antitubercular drugs contain small proportions of drug resistant mutants. If inadequate drug combinations are used, these mutants are likely to replace susceptible bacilli and give rise to drug resistant disease. The effectiveness of drugs in preventing the emergence of acquired resistant mutants depends on the extent to which they can inhibit bacilli continuously, whatever their rate of metabolism even when there is some irregularity in drug intake. Isoniazid and rifampicin are the most effective drugs in this category, streptomycin and ethambutol are slightly less active, pyrazinamide is least effective.

Isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol are, therefore, effective, when given intermittently(9).

The use of isoniazid for the preventive therapy of tuberculosis has been established through a series of clinical trials and the reduction in tuberculosis attributable to treatment with isoniazid ranged from 25-92%(10). The variation in effectiveness is explained by the amount of isoniazid actually ingested. Tuberculosis preventive therapy employing several drugs with potent sterilizing properties, like rifampicin and pyrazinamide given for periods as short as 2 months may be as effective as isoniazid given for 6-12 months. Rifampicin alone may be more effective than isoniazid even when given for a shorter period of time. Although there have been no studies of preventive therapy among those with HIV infection, 12 months of isoniazid preventive therapy is recommended for co-infected persons.

Kamlesh Chopra,
Chairperson, Tuberculosis Chapter of IAP and Director-Professor, Department of Pediatrics, Maulana Azad Medical College, New Delhi 110 002.

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