Modern Management of Pulmonary Tuberculosis

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The drug treatment of pulmonary tuberculosis in Britain is in the process of a reappraisal between one standard regimen and another: the highly effective 9-month regimen of rifampicin and isoniazid supplemented with either ethambutol or streptomycin for the first two or three months (*see this Journal*, February 1980) is being challenged by an equally effective 6-month regimen. This is also based on rifampicin and isoniazid throughout but includes pyrazinamide in addition to streptomycin or ethambutol for the first 2 months of intensive treatment. Both regimens are used at present and patient compliance with either is satisfactory under controlled trial conditions. This article concentrates on the newer 6-month regimen which is likely to be preferred for most patients on grounds of anticipated improved compliance and reduced cost due to its shorter duration. Furthermore, because elimination of tubercle bacilli is more rapid in the pyrazinamide-containing regimen, there is less risk of therapeutic failure if the patient does not complete the course of treatment.

THEORY

Variation in the metabolic activity of bacilli in the lesions of untreated patients affects their susceptibility to the action of different drugs. Actively metabolizing bacilli are rapidly killed by isoniazid, whereas rifampicin and pyrazinamide are highly effective against slowly metabolizing, semi-dormant bacilli which may persist in conditions of low oxygen and pH. Pyrazinamide has a special facility for bactericidal activity in the acid environment that may occur in early acute inflammation and also within macrophages, while rifampicin is distinguished by the speed with which its bactericidal action starts so that it is able to eliminate bacilli which metabolize briefly and intermittently.

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Drug resistance does not develop during treatment with two or more effective antituberculosis drugs, and in Britain the frequency of initial drug resistance is only 2 or 3%, usually confined either to streptomycin or to isoniazid. By including ethambutol or streptomycin in the regimen for the early phase of intensive drug therapy the risk of treatment failure due to initial drug resistance or to the emergence of resistance during chemotherapy is slight.

TREATMENT REGIMENS [BNF 5.1.9]

From these theoretical considerations there has evolved a highly effective 6-month regimen which comprises a 2-month initial phase of intensive daily treatment with four drugs (rifampicin, isoniazid and pyrazinamide plus *either* ethambutol *or* streptomycin) followed by a 4-month continuation phase with daily rifampicin and isoniazid. Alternatively the drugs may be given intermittently twice or three times weekly throughout, or daily during the initial phase and intermittently during the continuation phase. The usual daily dose schedules for adults are as follows:

rifampicin 600mg (or 450mg for those less than 50kg body weight) in a single oral dose on an empty stomach before breakfast, plus isoniazid 300mg daily; it is best to give rifampicin and isoniazid in a combined preparation (*'Rifinah'* or *'Rimactazid'*) to avoid inadvertent therapy with a single drug; pyrazinamide in a single daily dose of 1.5g for those less than 50kg body weight, 2g for those of 50 to 74kg and 2.5g for those of 75kg or more; and ethambutol 25mg/kg body weight in a single oral dose. This dosage of ethambutol is the one used in controlled trials of the 6-month regimen, although widespread use of ethambutol at the lower dose of 15mg/kg body weight appears to be satisfactory in the standard 9-month regimen, and may reduce the risk of unwanted effects. If streptomycin is substituted for ethambutol during the initial phase it is given daily in an intramuscular dose of 1g (0.75g in patients 40–60

years of age and smaller doses based on measurements of plasma streptomycin concentrations in patients over 60 years of age).

UNWANTED EFFECTS FROM TREATMENT

These are rare in patients younger than 35 years of age but become increasingly common with age. Rifampicin is the most frequent offender, causing anorexia, nausea and occasionally vomiting after the morning dose, but these symptoms usually subside after several days and the patient should be encouraged to persist with treatment unless prostrated. A more important toxic effect of rifampicin is hepatitis, and patients with liver disease, alcoholics and the elderly are particularly at risk. Liver function tests should be performed before starting treatment and repeated at intervals in those with impaired function. An asymptomatic rise in serum transaminase level may be transient and of no consequence, but if the serum bilirubin increases and the patient becomes symptomatic rifampicin must be withdrawn. All patients should be warned to stop treatment and inform their doctor if jaundice develops. Rifampicin is a hepatic enzyme inducer and increases the rate of metabolism of some drugs including warfarin, corticosteroids and oestrogens. The metabolism of the oestrogenic and progestogenic components of oral contraceptive 'pills' is also increased and women should be warned that this form of contraception becomes ineffective and an alternative method should be used (see also *this Journal* December 1983).

The most important unwanted effect of isoniazid is peripheral neuropathy which is prevented by the administration of pyridoxine 10mg daily throughout treatment. Some physicians therefore give pyridoxine routinely to all isoniazid-treated cases, but most reserve it for patients at special risk such as alcoholics and severely malnourished individuals. Central nervous effects of isoniazid include insomnia, restlessness and loss of memory, while fits may be precipitated in previously stable epileptics. Muscle pains, arthropathy and 'frozen shoulder' sometimes occur. Isoniazid can also cause hepatitis, but does so much less frequently than rifampicin.

The dangers of optic neuritis from ethambutol and of ototoxicity from streptomycin are well known, but the risk of ocular toxicity with ethambutol is small at the doses used. Both drugs are excreted by the kidneys and renal function must be checked before starting treatment. Ethambutol must be used with caution in those who may be slow to recognize visual deterioration, eg the very young or the aged, and all patients must be warned to report immediately the slightest impairment of vision when treated with this drug.

Pyrazinamide can cause arthralgia mainly affective the shoulders, knees and fingers during the first few weeks of administration, associated with a high serum uric acid level. It often improves spontaneously or can be treated with aspirin or allopurinol. Pyrazinamide is contraindicated in patients who suffer from gout and these patients should be given the standard 9-month regimen. Historically the most serious and important complication of pyrazinamide was hepatitis, but with the current dosage regimens it is infrequent, and in a controlled trial hepatitis occurred no more commonly with the two regimens which included pyrazinamide than with the one which did not.

MILESTONES OF TREATMENT

There are four crucial stages in the treatment of pulmonary tuberculosis: the pre-treatment stage when hepatic and renal function are assessed, the regimen most suitable for that individual is chosen, and the patient is taught about his disease and its treatment; the first two weeks when the patient accustoms himself to regular drug therapy and the risk of unwanted effects is highest; the two month milestone when the sensitivities of the infecting organism become available so that the original choice of regimen can be ratified and instructions given to transfer from the 4–drug combination of the initial phase to the 2–drug combination of the continuation phase; and finally, the 6–month milestone when all treatment is discontinued unless a longer course is advisable because of evidence of poor compliance or unduly slow sterilization of the sputum. Relapse is very unlikely in patients who have conscientiously taken the full course of chemotherapy, and in such cases it is reasonable to discharge the patient on completion of treatment provided that instructions are given about symptoms which might indicate reactivation such as persistent cough, haemoptysis, sustained weight loss or night sweats, and how to seek further advice if they occur.

Where there has been initial drug resistance or any doubt about the patient's compliance with therapy it is better to review the patient occasionally for two years following the end of treatment since relapse is most likely to occur within this time.

The published evidence shows that even in patients infected with organisms resistant to isoniazid or streptomycin or both, failure of chemotherapy or subsequent relapse are very rare if the standard 6–month regimen is completed. If, at the 2–month milestone, the organism turns out to be insensitive, for example to isoniazid, it is advisable to continue ethambutol for the total period of six months.

ROLE OF THE FAMILY DOCTOR

The continued decline in the incidence of pulmonary tuberculosis in the country has made it an uncommon disease which is sometimes overlooked. Recent surveys shows that many elderly patients die from the disease before the diagnosis has been made, or in the early weeks of treatment. The most important role of the family doctor is to be suspicious of pulmonary tuberculosis always, but most particularly in the elderly in whom the disease often mimics or coexists with commoner conditions such as lung cancer or chronic bronchitis. Where suspicion is aroused immediate referral is necessary to a thoracic medicine unit where microbiological examination of the sputum and radiological assessment are carried out, and staff are on hand to supervise treatment of positive cases, trace contacts and organize BCG vaccination and chemoprophylaxis where necessary. Notification of a case of tuberculosis is required of any doctor who makes a positive diagnosis, and although the responsibility commonly falls to hospital doctors it is still incumbent on family practitioners to notify the District Medical Officer for Environmental Health of patients whom they have themselves diagnosed on the basis of a positive sputum examination. Because treatment is complex it should be initiated and carried through by a thoracic medicine specialist who is often the only clinician in the district who has had adequate experience of this increasingly uncommon disease. Mistakes in treatment are best avoided by prescribing drugs from the chest unit unless the liaison between the specialist and the family doctor is an exceptionally close one. Nevertheless it is vital that family doctors are fully informed of the details of treatment and possible unwanted effects which may arise. General practitioners can then respond reassuringly to difficulties or anxieties experienced by the patient and either encourage continued compliance with the regimen, or obtain early specialist advice when a change of therapy appears necessary or compliance is failing.

SPECIAL CIRCUMSTANCES

Pregnancy alters the choice of drug regimen because streptomycin is ototoxic to the fetus and rifampicin may be teratogenic. Isoniazid is safe provided that pyridoxine [BNF 9.6.2] is given simultaneously to avoid a possible risk of psychomotor retardation or convulsions in the newborn infant. There is no evidence of teratogenicity from ethambutol or pyrazinamide (although the second-line drug prothionamide is teratogenic and should be avoided). Women should be advised to avoid pregnancy while receiving antituberculosis chemotherapy and it is logical to exclude streptomycin when treating women of child-bearing age in case they do not follow this advice. Rifampicin is too important a component of chemotherapy to be withheld because the patient might become pregnant, but if she does, rifampicin should be withdrawn unless there are particularly strong grounds for its continuation such as an isoniazid-resistant infection or very extensive disease. Treatment should then be continued with at least two and preferably three drugs during the first 2-month period of intensive chemotherapy (eg isoniazid with pyridoxine supplements, ethambutol and pyrazinamide), and 2 drugs during the continuation phase (eg isoniazid and ethambutol). Rifampicin can be reintroduced once the pregnancy is over but the total duration of treatment and surveillance may need to be prolonged depending on the severity of the infection.

Renal failure poses special problems in the treatment of pulmonary tuberculosis because drugs normally excreted by the kidneys are liable to accumulate to toxic levels. Fortunately, rifampicin can be given in normal dosage because it is excreted in the bile, and isoniazid needs no dosage adjustment except with a creatinine clearance of less than 10ml/min, in which case the adult daily dose should be reduced to 200mg. Provided that there is little likelihood of initial drug resistance to isoniazid the safest solution in patients with renal failure is to give

standard doses of rifampicin and isoniazid plus supplementary pyridoxine for a minimum of nine months. In the presence of drug resistance or unwanted effects which necessitate a substitute for isoniazid or rifampicin, a possible alternative drug is streptomycin but it requires careful dose reduction to avoid toxicity, based on knowledge of the patient's creatinine clearance and plasma streptomycin concentrations which can be measured readily in most hospital laboratories. Ethambutol requires equally careful dosage regulation but plasma estimations are less easily available; if it is used, regular ophthalmological examinations should be carried out. There is little published information about the use of pyrazinamide in renal insufficiency.

CHEMOPROPHYLAXIS

Chemoprophylaxis is the preventive treatment of apparently healthy people who have a high risk of developing active tuberculosis judged by a strongly positive reaction to the tuberculin test. Its main justification is among contacts in whom tuberculin conversion is likely to have occurred recently, particularly children up to five years of age with grade 2–4 reactions to the Heaf multiple puncture skin test, and those between 5 and 15 years with grade 3 or 4 reactions. Because the Asian community in Britain has a comparatively high annual notification rate chemoprophylaxis is recommended for contacts of an Asian index case with reactions of grades 2–4 up to the age of 15 years, and can also be justified up to the age of 35 years if compliance is assured. The treatment is with isoniazid alone in a daily dose of 300mg in adults or 5–10mg/kg in children to a maximum of 300mg for one year. The risk of isoniazid-induced hepatitis is very small in individuals under the age of 35 years unless they are alcoholics, and the main problem of chemoprophylaxis is to ensure continued compliance in people who are not ill.

CONCLUSION

There is reliable evidence that six months chemotherapy for pulmonary tuberculosis using a pyrazinamide-containing regimen is just as effective as the earlier standard regimen lasting nine months, but careful supervision is still required. The indications for chemoprophylaxis with isoniazid among young people in this country ae now better defined but each case must be considered individually.

Editorial Note

The authors of the paper entitled "Maple Syrup Urine Disease in Bahrain." (BMB 7; 3, 1985) should be listed as Dr. Hadi Khalil Ebrahim and Dr. Akbar Mohsin Mohammad, rather than as printed. The order was inadvertantly reversed during printing. The BMB apologise to Dr. Hadi Khalil for accidentally relegating him to the position of second author, since he was in fact, the principal author. References to this paper should take this revision into account.