Treatment of Tuberculosis

M. McNICOL, MB, FRCP
Physician, Central Middlesex Hospital, London

Several aspects of the present treatment of tuberculosis will be considered, including the available drugs, the choice of suitable combinations, recent changes from 'classical' standard chemotherapy, the need for careful supervision, the problems and adverse effects that may arise, the treatment of non-pulmonary disease, costs of treatment, and the future trends in treatment.

Available Drugs

The anti-tuberculous drugs can be classified into bactericidal drugs such as the potent rifampicin and isoniazid, the less potent streptomycin and pyrazinamide, and bacteriostatic drugs that are significantly less potent anti-tuberculous agents. This group includes PAS, ethambutol, thiacetazone and all the other anti-tuberculous drugs at present available.

The following considerations are important in devising a treatment regime:

1. At least two drugs must always be given in combination.
2. Wherever possible the combination should include one first order bactericidal drug.
3. In the initial combination, it may be necessary to include more than two drugs if sensitivity tests in the local population have shown a high incidence of organisms with primary resistance.

Standard Treatment

The standard regime used in the UK at present (*Lancet*, 1976) is daily treatment for nine months with a combination of rifampicin 450 to 600 mg and isoniazid 300 mg. In addition, ethambutol is given in a dose of 15 to 25 mg/kg daily for the first two months. This regime has been found to be well tolerated and highly effective, 85 per cent of the patients becoming sputum negative by three months. After nine months of treatment there were no relapses during follow-up.

Previous 'classical' chemotherapy included isoniazid, streptomycin and PAS for 18 months. Isoniazid 300 mg and PAS 12 mg were given throughout the treatment in a twice daily dosage scheme. For the first three months streptomycin 0.75 to 1.0 g by intramuscular injection was given on either five or seven days a week. Properly supervised, this regime was highly effective, but sputum conversion was slower. The disadvantages include the need for injections, the longer period for patient compliance, and the less acceptable daily preparation of PAS.

Difficulties with chemotherapy will arise if there is a high incidence of primary resistant organisms, if treatment is inadequately prescribed, or if patient compliance is poor so that acquired resistance occurs during treatment. Failure to comply with treatment has been increasingly recognised as a problem, although it is likely that it is no more frequent now than it was with earlier regimes. However, as treatment regimes are being developed to use fewer doses of drugs it is increasingly important to ensure that all doses are taken.

Adverse effects of drugs remain a significant though rather less important cause of problems in treatment. With the 'classical' regime, approximately one-third of the patients experienced hypersensitivity reactions but these are much less frequent with the rifampicin-isoniazid regime.

Supervision of Treatment

Starting anti-tuberculous therapy is relatively easy; carrying it through to its appropriate completion, which is essential for its success, is a much more difficult task. Adequate supervision of the patient does not require hospital admission. The diagnosis can be established by investigations, and treatment can be started at an out-patient clinic unless there is a specific indication for admission. Treatment should be reviewed at four weeks to check for compliance with medication or for any other problems that may have arisen and for medical and radiological assessment of improvement. If there are no problems the patient is then reviewed at 3, 6, and 9 months after the start of therapy. If, at nine months, clinical and radiological progress has been satisfactory, there is no doubt that the drugs have been reasonably effectively taken, and the disease appears to be arrested, it is probably safe to discharge the patient from further follow-up. If there is any cause for concern, a limited follow-up period of two years should be adequate, as most relapses will occur during that time.

An efficient organisation is essential to ensure that all defaulters from treatment are pursued; where necessary, patients should be visited at home for adequate supervision of their drug therapy.

Adverse Effects

Adverse effects tend to be troublesome with anti-tuberculous chemotherapy because of the prolonged period of treatment. Hypersensitivity reactions may occur with any of the drugs and the incidence is maximal two to three weeks after the start of chemotherapy. In addition, specific toxic effects may occur with all drugs.

Patients should be warned that rifampicin commonly gives a purple colour to the urine. Rifampicin induces hepatic enzymes and thus reduces the efficacy of oral contraceptives so that alternative methods of con-

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traception should be used during treatment. It is not yet clear whether this drug is teratogenic but it should not be prescribed during the first trimester of pregnancy. Elevation of serum levels of hepatic enzymes is common during the first few weeks of rifampicin therapy and, rarely, a true hepatitis may develop. Hypersensitivity reactions are not infrequent with rifampicin, if it is used in intermittent regimes, but are uncommon with daily treatment (Poole *et al.*, 1971). Hepatitis due to anti-tuberculous drugs has been thoroughly reviewed recently (Girling, 1978). With isoniazid, hepatitis is less frequent but may cause major difficulties in treatment and fully developed isoniazid hepatitis carries a small but significant mortality. Isoniazid in high doses may also induce pyridoxine deficiency, but this is easily avoided by giving a small daily dose of pyridoxine to all patients receiving isoniazid.

The major specific toxic effect of ethambutol is optic neuritis which is reversible if treatment is stopped as soon as symptoms appear. The incidence is much less frequent if a dose of 15 mg/kg a day is used rather than the higher dose of 25 mg/kg and there appears to be no loss of clinical effectiveness. Streptomycin frequently causes sensitivity reactions and, in addition, causes ototoxicity which is often irreversible after cessation of therapy. Toxicity is especially likely to occur in patients with impaired renal function. Pyrazinamide is a relatively safe drug but may produce hepatitis, although this is uncommon if the dose is kept below 1.5 g a day.

Costs

The costs of treatment for tuberculosis are not inconsiderable. For drugs alone, a nine month course of treatment with rifampicin, isoniazid and ethambutol for a patient of average weight costs approximately £250 compared with £150 for 18 months' treatment with isoniazid, PAS and streptomycin. (Drug costs are based on those in the current edition of MIMS.) Recently, there has been a substantial narrowing of the difference between the basic drug costs of rifampicin-isoniazid treatment compared with previous standard regimes so that in the UK there is little reason on grounds of cost to choose other regimes. Currently, attempts are being made to develop a shorter course of treatment requiring fewer doses of drugs. Preliminary work has shown that such regimes have a high, if not yet fully acceptable, efficacy. They will be based on rifampicin and isoniazid and will require increased supervision to ensure that all the doses of the drugs are taken.

In concluding this brief review of anti-tuberculous chemotherapy it is important to stress that rifampicin-isoniazid regimes are well tolerated by patients and are highly effective but still require skill and care in their usage. Careless anti-tuberculous chemotherapy, usually the result of inadequate supervision, is liable to provoke the emergence of drug-resistant strains of organisms, with untoward consequences for individuals and for the community.

References

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