Short Course Chemotherapy in Tuberculosis

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Among the greatest medical achievements of the 20th century has been the discovery of anti-tuberculosis drugs which are capable of curing every patient suffering from tuberculosis. The use of mass chemotherapy has resulted in a spectacular decline of the disease in technically advanced countries. Unfortunately mass chemotherapy has proved a failure in most developing countries and no country has managed to eradicate tuberculosis. The main reason for failure is that the very long duration of drug treatment, required to cure tuberculosis, has proved unacceptable to patients. *The discovery of rifampicin has opened up a new era, making possible a cure of tuberculosis in months rather than years.* The purpose of this article is to describe the development and potential of short-course chemotherapy.

Assessment of drug regimens in controlled trials

Drug regimens are studied by two types of investigations, both of which are essential. The first is a meticulously conducted controlled trial under ideal programme conditions in carefully selected and co-operative patients comparing the new regimen with an established one. This shows the maximum potential of the regimen. It is a mistake to think however that these results are the same as those obtained in normal field conditions in a community. To ascertain this, it is necessary to undertake additional studies under field conditions amongst unselected patients to see how the programme works in practice in the highly different circumstances in different communities.

The failure of standard long course chemotherapy

Standard long course chemotherapy has been widely used throughout the world during the last 30 years. It comprises daily isoniazid with a companion drugs to prevent resistance, this companion drug being either ethambutol, PAS or

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thiacetazone. For the first one or two months a third drug streptomycin is given. Drug must be taken for one and half year to ensure freedom from relapse. *Continuation for only six months results in about 60% relapse. Field studies in South India, Kenya and several other developing countries show that this long course treatment usually fails, more than half the patients having defaulted before the end of the year. It is particularly after six months that the patients tend to default.* Short course chemotherapy aims to avoid failure because only six or nine months co-operation with treatment is necessary.

Basic mechanisms of short course chemotherapy

The choice of drugs for short course chemotherapy is based upon recent understanding of the different populations of tubercule bacilli which exist in tuberculous infection. At the beginning of treatment many bacilli are rapidly dividing. These are rapidly killed by the three most bactericidal drugs which are isoniazid, rifampicin and streptomycin.

There are other populations in which the organisms are dividing slowly. These are killed less rapidly by drugs. They are the so called persisters. These organisms are responsible for relapse. Some persisters are organisms under acidic conditions which are specially killed by pyrazinamide.

Another special population of persisters are organisms which have only short bouts of metabolism. These are rapidly killed by rifampicin which is unique in its property of rapid bactericidal action. Thus, pyrazinamide and rifampicin are known as sterilizing drugs because they deal with persisters which are responsible for relapse. (see Fig. 1).

Short course chemotherapy requires drugs which are bactericidal, isoniazid and rifampicin being particularly important. It also requires sterilizing drugs, rifampicin and pyrazinamide being the most important of these. Bacteriostatic drugs, ethambutol, PAS and thiacetazone have little value in short course chemotherapy.

Trials of short course chemotherapy

The first validation of the effectiveness of short course chemotherapy was the study by the East African — British Medical Research Council published in 1972 showing that daily streptomycin, isoniazid and rifampicin given for six months only was effective and had a negligible relapse rate.

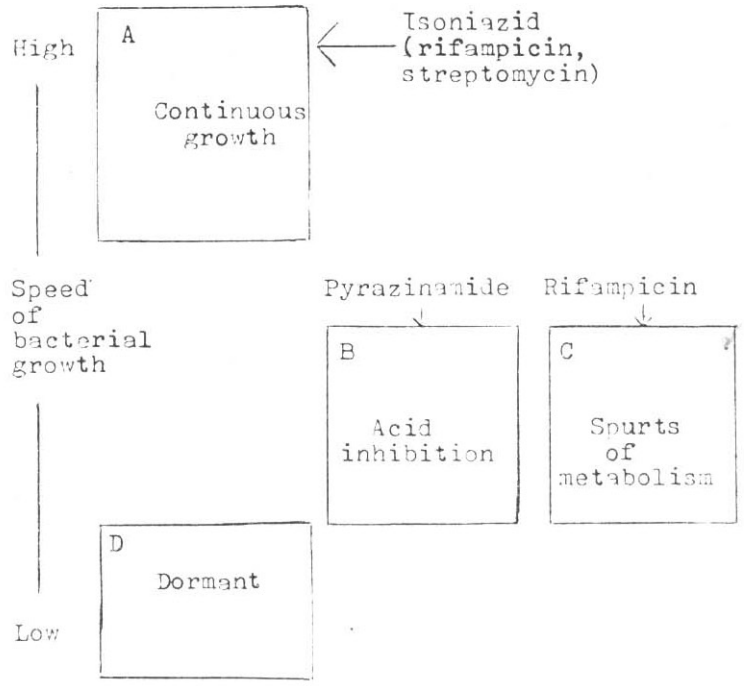

Fig. 1. Special bacterial populations.

Nine months short course

Encouraged by these observations, the British Tuberculosis Association set up a Committee in 1972, of which I had honour of being Chairman, in order to undertake a field study on short course chemotherapy to find the optimum duration for British patients. It was a true field study being undertaken in many different hospitals and chest clinics throughout Britain. The regimens studied all contained rifampicin and isoniazid given by daily self-medication. Four durations were studied, 6, 9, 12 or 18 months. An initial triple phase was given for the first two months, the third drug being either streptomycin or ethambutol. The results show that 6 months treatment resulted in a relapse rate of 6%. There was no relapse in the 9 months regimens. Streptomycin and ethambutol were equally effective as the initial third drug. *Thus, 9 months short course was recommended by British Tuberculosis Association for treatment of pulmonary tuberculosis and it is now used widely.* It consists of rifampicin and isoniazid daily for 9 months with either streptomycin or ethambutol for the first 2 months. (See Table I for details and Table II for drug dosage).

Six months short course including pyrazinamide

There is evidence from clinical trials that pyrazinamide is valuable in short course chemotherapy as a sterlizing drug. The British Tuberculosis Association used pyrazinamide in a six months regimen. Rifampicin and isoniazid were given daily for six months. During the first two months, an initial intensive phase of four drugs was given — the additional drugs were pyrazinamide with either streptomycin or ethambutol. The results of this study published in 1982 show that this was highly effective with negligible relapse. *Six months regimens are now very popular in Britain and comprise ethambutol, isoniazid, rifampicin and pyrazinamide for two months followed by rifampicin and isoniazid for remaining 4 months.* (See Table I and II). Its advantages are that it is short, highly acceptable and relatively non-toxic. Moreover, it is effective in patients whose pretreatment organisms are resistant to streptomycin and isoniazid. A higher proportion of patients who absconded early are likely to be cured as compared with those who absconded from regimens which do not contain the sterilizing drugs rifampicin and pyrazinamide.

Special aspects of pyrazinamide

The dose of pyrazinamide is 30mg per kilo and its duration is two months (Table II). A controlled study in the Britain showed that the use of pyrazinamide did not cause an excess of liver toxicity compared to regimens without pyrazinamide. However countries with frequent liver diseases may have more toxicity with pyrazinamide and pilot studies of toxicity may be required. *Pyrazinamide is of little value in the continuation phase of chemotherapy and its use can be limited to the first two months.*

The role of rifampicin in continuation therapy

Rifampicin is a powerful bactericidal and sterilizing drug. Studies of rifampicin in continuation therapy indicate that it plays an important role in this. However, it is an expensive drug and for this reason the total dose may need to be minimized. A combination of streptomycin, isoniazid, rifampicin and pyrazinamide given daily for first two months of treatment is so effective that continuation therapy need not contain rifampicin provided that duration of continuation phase is increased to 8 months. Thus isoniazid and thiacetazone or isoniazid alone continued for six months after initial streptomycin, isoniazid, rifampicin and pyrazinamide gives very satisfactory results (see Table I) providing a relatively cheap 8 months treatment.

Fully supervised intermittent short course chemotherapy

Even the best short course regimen will fail if patients do not take medications. For patients who are not willing or unable to undertake reliably self-medication, intermittent therapy giving drugs 2 or 3 times weekly, enables every dose to be supervised. Patients may get the drugs by attending clinics or having these administered to them either at place of work or at home.

Several regimens are available which give the advantage of full supervision with short duration treatment. Streptomycin, isoniazid, rifampicin and pyrazinamide (or) ethambutol, isoniazid, rifampicin and pyrazinamide given three times a week is effective in six months. A useful partial intermittent regimen consists of streptomycin, isoniazid, rifampicin and pyrazinamide given daily for 2 months followed by isoniazid, rifampicin given twice weekly for the remaining 4 months (see Table I).

TABLE I.

SHORT COURSE REGIMENS

Initial intensive phase		Continuation phase	Total duration of regimen
Drugs and frequency	Duration (months)	Drugs and frequency	
Daily Regimens			
EHR daily	2	HR daily	9
SHR daily	2	HR daily	9
SHRZ daily	2	HR daily	6
EHRZ daily	2	HR daily	6
SHRZ daily	2	HT daily	8
Intermittent Regimens			
SHRZ 3 times weekly	6	—	6
EHRZ 3 times weekly	6	—	6
SHRZ 3 times weekly	2	HR 3 times weekly	6
SHRZ daily	2	HR 2 times weekly	6

Drugs in Table I and II H = isoniazid; R = rifampicin; Z = pyrazinamide; S = streptomycin; E = ethambutol; T = thiacetazone.

Dosage of drugs

It is important that correct dose of drugs is given if maximum effect is required and toxicity avoided (see Table II for details of dosage).

TABLE II.

DRUG DOSAGE

Drugs	Weight	Dosage for adults		Daily dose for children
		Daily	Intermittent	
Isoniazid	—	300mg	15mg per kg	10mg per kg
Rifampicin	less than 50 kg	450mg	600mg	10–20mg per kg
	50 kg or more	600mg	600mg	—
Streptomycin	less than 50 kg	750mg	750mg	20mg per kg
	50 kg or more	1g (750mg in over 40 years of age)	1g	—
Pyrazinamide	less than 50 kg	1.5g	3 times a week 2.0g twice a week 3.0g	40mg per kg
	50 kg or more	2.0g	3 times a week 2.5g twice a week 3.5g	—
Ethambutol	—	25mg per kg for 2 months, then 15mg per kg.	—	As for adults if age 12 years or more

Cost of drug regimens

A major consideration for developing countries is the cost of drugs for the limited national health budget or for the poor patient who has to pay for

drugs. Rifampicin is unfortunately relatively expensive. However, it must be understood that the cheaper long course chemotherapy regimens often fail and the cost may ultimately prove considerable because the patient is likely to relapse and need retreatment and in the meantime may spread infection to other members of the family and produce more patients requiring treatment.. By involving the family in contributing the cost of treatment, it is often possible to obtain money in the poorer family. Especially cheap regimens consist of an initial phase of streptomycin, isoniazid, rifampicin and pyrazinamide for two months followed by either rifampicin and isoniazid twice weekly for another 4 months or isoniazid and thiacetazone for another six months (see Table I). Bulk buying of drugs by Health Services considerably reduces cost and aids in the provision of drugs free for the patients unable to afford to pay for themselves.

Patient compliance

The best regimen will fail if the patient does not take it. Therefore, motivating the patient taking a drug is as important as prescribing the correct drug regimen. The patient should always be told at start of treatment the necessary duration of treatment and the reasons for it. Many patients stop taking drugs once they feel better and the need to continue the drugs long after they feel well must be clearly understood by the patients and their family. It is specially important to involve the family in the treatment so that they can encourage and support the patient. Short course chemotherapy renders the patient non-infectious almost immediately the drugs are started. This safeguards the family, makes segregation in hospital unnecessary and enables the patient to continue his normal occupation, so helping to pay for drugs. Spread of disease is halted, hospital treatment is unnecessary and money can be saved on hospital beds and spent on drugs and on an effective programme of supervision of chemotherapy preferably in primary health care centres, using para-medical primary health care workers to motivate and supervise patients on clinic visits and in their homes. *Chest X-ray and ESR tests are not required during chemotherapy: the money might be spent on the provision of drugs. Inspite of our best efforts, patients default early. That is why initial intensive chemotherapy with (1) streptomycin, isoniazid, rifampicin and pyrazinamide or (2) ethambutol, isoniazid, rifampicin and pyrazinamide are so important because these regimens will cure about 60% of patients in 2 months only.*

Conclusion

There can be little justification for continuing to use long course chemotherapy because of the high failure rate in developing countries. Short course chemotherapy is likely to cure more patients. Effective chemotherapy is the best method of controlling tuberculosis in a country. Treatment is the best prevention because it reduces the source of infection. The epidemiologists tell us that the outlook for tuberculosis in developing countries during the next 10 years is indeed grave and it is estimated that there will be 50 million new cases, of whom 2/3rd will die. I believe that with the proper use of short course regimens, we can now attain cure in the majority of patients and that tuberculosis can be defeated in the developing countries.