Infectious Diseases

Rifadin — its rôle in the treatment of Tuberculosis

Over the last thirty five years chemo-antibiotic therapy has radically changed the treatment and thus the history of tuberculosis.

The introduction of isoniazid into antituberculosis therapy led to the hope that the epidemiological cycle could be decisively interrupted, with progressive reduction of the reservoirs of chronic cases and a consequent simultaneous decline in the number of new ones.

But we now know that these expectations have been only partially achieved.

In fact, two difficulties arose when antituberculosis chemoantibiotic treatment was introduced — the insufficiency of specialised infrastructures and the limited availability of economic resources.

It became obvious that the only realistic approach was generalised out-patient therapy. Saving on hospitalisation costs should only be possible with early detection of infectious patients and provision of acceptable supervised treatment to render the patient non-infectious.

This can only be achieved to the best advantage by our examination of the drug action in short-course chemotherapy.

The two cardinal objectives in short-course chemotherapy of tuberculosis are: to kill dividing bacili; and to kill "persisting" bacilli

Both objectives can only be attained by use of bactericidal drugs such as rifampicin, pyrazinamide, isoniazid and streptomycin.

These potent bactericidal drugs have this ideal "sterilising" activity because when used together they kill the large population of extracellular bacilli which are found in the macrophages.

The latter, if not killed, will cause relapse in a patient who may appear "cured" when he has had several sputum specimens found to be culture negative.

It is only in the years of follow-up after treatment that one knows whether treatment has been successful or not.

Relapse rates have been found to be lowest only in short-course regimens which contain the bactericidal drugs rifampicin, pyrazinamide, isoniazid and streptomycin.

What is the role of bacteriostatic drugs such as ethambutol in comparison with a potent drug such as pyrazinamide?

Wallace Fox of the British MRC commented on this when assessing a trial in Hong Kong in which pyrazinamide replaced ethambutol both in the daily (SHRZ) and intermittent phase (S_2 H_2 Z_2).

His own words are: "Thus, pyrazinamide is again demonstrated to be a drug with both potent bactericidal and sterilising activities and I interpret the findings with the ethambutol regimen as indicating that the ethambutol contributed nothing in either respect".

In fact, the only role that can be found for it in the current standard British regimen for TB treatment of nine months rifampicin plus isoniazid supplemented for the first two months with either streptomycin or ethambutol is as the "companion" drug for the first two months, which serves to prevent the emergence of bacterial resistance to either of the potent bactericidal sterilising drugs — rifampicin and isoniazid.

TB is curable within months and most patients can be treated at work. TB is therefore no longer a danger to the patient nor to other people (contacts) provided that the disease is diagnosed as early as possible and that adequate treatment is given under supervision for as long as necessary.

Diagnosis is best done by X-ray, tuberculin skin testing, sputum examination, histology and clinical trial (radiological improvement, constitutional improvement with resolving pyrexia and reducing sedimentation rate.

There are some interesting TB

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Regime 1 (State Health)

Drug	Dosage	Administration	Duration
Streptomycin	Age < 50 yrs 1G Age > 50 yrs ½G	Once daily or 3 x/week	4 - 6 months
Rifampicin	Body mass < 50 KG 450 mg Body mass > 50 KG 600 mg	Once daily (Mon - Fri)	6 months
Isoniazid	400 mg	Once daily (Mon - Fri)	6 months
Pyrazinamide	2 G	Once daily (Mon - Fri)	2 months

treatment regimes among several currently used. One is Regime 1 of the State Health Department.

With this regime the patients should be non-infectious within a few days and fit to return to work unless other complications are present, for which further hospitalisation may be necessary.

The efficacy of TB regimes cannot be measured in terms of sputum conversion from positive to negative; but by the relapse rate — i.e. a recurrence of tuberculosis at any time after the completion of a successful and acceptable course of therapy.

The relapse rates for Regime 1 are of the order of 5% or less when patient compliance has been assured by supervision of each dose of medication, provided that the patient harbours organisms sensitive to each of the drugs.

It has been shown in numerous trials that patient compliance is inversely proportional to the duration of a treatment regime. Relapse rates become unacceptably high when regimes are prolonged beyond six months and when supervision is not strict.

This has led to the search for effective short-course regimes with a duration more likely to ensure compliance and a low default rate with an ensuing low relapse rate and lowered cost in drugs, administration and follow-up of patients who have completed a course of TB chemotherapy.

When reviewing costs, the cost-effectiveness of drug regimes must be included in the accounting. With the very effective 4 bactericidal drug regimes of six months duration, failure rate and relapse rate are acceptably low, and not only is the high cost of hospitalisation saved; but 95% or more of patients will not require retreatment.

The patient who continues at work is not a burden to the tax payer because he and his family do not require social service payments.

Tuberculosis treatment with 4-drug bactericidal regimes is effective. How safe are these drugs?

Adverse reactions of TB drugs

Isoniazid

Provided dosage is kept within recommended limits, adverse effects will be rarely encountered. There may occasionally be central and peripheral nervous system effects. Hepato-cellular juandice may result as a hypersensitivity phenomenon.

Pyridoxine (vitamin B6) is not often necessary as a supplement to counteract peripheral neuritis.

Rifampicin

Because it has a true mycobactericidal action, rifampicin has revolutionised TB treatment through faster and lasting therapeutic efficiency.

There may be transient elevation of serum transaminases which usually return to normal levels even when treatment with rifampicin is not discontinued.

Jaundice resulting from severe hepatic dysfunction may occasionally occur, particularly when isoniazid, rifampicin and pyrazinamide are used together; but this is more likely to occur in patients with a history of liver dysfunction.

Purpura, thrombocytopenia, abdominal pain with nausea and sometimes vomiting and diarrhoea are relatively rare.

Toxicity has not proved to be a problem. Patients taking corticosteroids, hypoglycaemic agents, anti-coagulants and some other drugs should have the dosages monitored and adjusted and women taking oral contraceptives should use other contraceptive methods.

Patients should be advised that urine, tears and sweat may have a reddish discolouration.

Pyrazinamide

The most common and important adverse effect is hepatitis. Gouty arthritis occasionally develops; arthralgias, mild anorexia and malaise may also develop; but these do not require withdrawal of the drug.

Streptomycin

Particularly in patients, 50 years or over, streptomycin may affect the vestibular portion of the Eighth Cranial nerve, and the auditory branch may be affected to a lesser extent.

Vertigo, nausea, vomiting and headache may herald vestibular damage. Tinnitus is the first symptom of auditory damage, and permanent hearing loss may result if the drug is not discontinued.

Impairment of renal function is rarely severe, but mild reactions as a result of tubular irritation are fairly common.

Pre-existing renal disease other than renal tuberculosis is a contra-indication to the use of streptomycin. Injections should be given intramuscularly to minimise local reactions.

Ethambutol

Sometimes has toxic effects on the optic nerve, with visual loss which is frightening and unpleasant, but usually transitory, although recovery after withdrawal of the drug may be slow.

Blurring and hazy vision may be followed by progressive decrease in visual acuity, contraction of visual fields, poor colour discrimination and central scotomas.

The dosage usually recommended is 25 mg per kilogram of body mass for not longer than five months based on the fear of visual impairment at this high dosage, since toxic symptoms commonly develop after six months of treatment with 25 mg per kilogram body mass.

Because ethambutol has a bacteriostatic effect, its role is limited to the prevention of emergence of resistance of bacilli to the main drugs rifampicin, isoniazid and pyrazinamide; but ethambutol does not help to shorten the duration of chemotherapy, so should not be used as a substitute for the bactericidal drugs in short-course regiments.

Conclusion

Considering all the available evidence, a six-month regimen would appear to be the optimum duration for all patients if the measure of success is to aim as near as possible to 100% cure.

Isoniazid and rifampicin are likely to be necessary throughout with pyrazinamide for an initial period of two months.

The advantage of regimens with four drug initial intensive therapy and isoniazid and rifampicin in the continuation phase is that if patients abscond relatively early in treatment, they stand a much better chance of being cured than if the regimes did not include pyrazinamide initially or rifampicin in the continuation phase.

References

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