


**Rifampicin in clinical use**

The development of rifampicin for clinical use has been followed by numerous clinical trials, mainly in tuberculosis.

To many who practise medicine in England, and in other countries fortunate enough to enjoy a stable and prosperous society, tuberculosis is a relatively rare disease and it is easy to forget that it remains a frequent cause of death and disability in the less fortunate countries in which occur some 15 million active cases of tuberculosis currently with 3 million deaths annually. Even in England the importance of the disease can easily be underestimated. In cities with many immigrants from Asia it is by no means uncommon. In Birmingham, with a population of just over 1 million, about 450 new cases still occur annually. More than half of the patients are immigrants, the majority young, whereas English-born patients are more often elderly, belonging to a generation heavily infected in early life. The disease is curable, given any reasonable chance. Failure results from very late diagnosis, serious complicating disease and failure to apply or take the chemotherapy. It is a tragedy that such effective chemotherapy for so serious a disease is not universally available to the millions who need it. We may hope that this will not always be so.

The medical profession can hardly be blamed for economic and political failings but must accept most of the responsibility for chemotherapeutic disasters.

Streptomycin and para-aminosalicylic acid were enormous advances in therapy but are not ideal for use on a massive scale since they are difficult to administer and supervise, the duration of treatment is long and both toxic and allergic reactions are frequent. The drug which tipped the scale against the tubercle bacillus was isoniazid since it is highly effective, cheap, easy to take and rarely causes toxic or allergic reactions in therapeutic doses. The series of careful clinical trials initiated by the Medical Research Council's Tuberculosis Research Unit left no doubt about the best use of these drugs. Unfortunately in many countries, particularly those with greater need for them, the drugs were often badly used and drug-resistant infections became fairly common. It is fortunate that in England the problem has been small.

Acquired drug-resistant infections are rare, mainly because patients who acquired drug-resistance in the early days of chemotherapy have either died or been subsequently cured by the use of more recently-developed drugs. Primary drug resistance is encountered mainly in immigrants and in most cases it is resistance to one of the older drugs such as streptomycin and presents no serious difficulty in clinical management.

Rifampicin is comparable with isoniazid in effect and acceptability. Daily treatment with 450 or 600 mg gives rise to little toxic or allergic trouble. Only about 1% of patients on 450 mg daily can be expected to develop jaundice and this, in most cases, is transient and of no serious consequence. A rise in serum transaminase levels, usually in the first month of daily treatment, has been reported in 21 to 29% of patients (Lees, Allan, Smith, Tynell & Fallon, 1971; Lal, Singhal, Burley & Crossley, 1972), but when 450 mg is used as the standard dose rather than 600 mg the rise in transaminase may be less frequent and more transient. The British Thoracic and Tuberculosis Association (1975) reported 3-6% of 802 patients who received daily isoniazid and rifampicin had adverse effects of sufficient severity to interrupt treatment and of these 2-4% were attributed to rifampicin. Personal experience suggests that using 450 mg even fewer significant adverse effects may occur.

Intermittent high dosage regimes using 1200 mg of rifampicin once or twice a week give rise frequently to "flu-like" reactions and jaundice (Poole, Stradling & Worlledge, 1971; Aquinas et al., 1972) and 20 to 40% of patients may acquire rifampicin-dependant antibodies which are significantly correlated with the "flu-like" reactions (Worlledge, 1975). Both the "flu-like" reactions and the
occurrence of antibodies are rare with daily treatment.

Clinical results of combined daily rifampicin and isoniazid are excellent (East African/British Thoracic and Tuberculosis Association, 1974; British Thoracic and Tuberculosis Association, 1975). It seems likely that only 9 months of such daily treatment will suffice to cure even extensive disease in virtually any anatomical site. The limiting factor at present to the elimination of tuberculosis is cost. While this is negligible against the background of the British National Health Service expenditure and is among the "best buys" in treatment, it is a serious problem for poorer countries where tuberculosis is still common. Surely it will not always be so! It is of the greatest importance that the enormous potential of combined treatment with isoniazid and rifampicin should be safeguarded until it can be fully used.

Isoniazid has been subject to abuse in tuberculosis, but in little else, since its spectrum of activity is narrow but the position is not quite the same with rifampicin which is active in vitro against many organisms, particularly staphylococci. There is a temptation to try rifampicin in other infections, especially severe pneumonias which could be tuberculous or staphylococcal. This temptation may be greatest in places where diagnostic facilities are poorest but where the consequences of such use could be particularly unfortunate.

Staphylococcal infections have presented a continuing challenge since the introduction of the sulphonamides and penicillin but there are several effective antibiotics available and the most difficult cases to treat often occur in sophisticated hospitals. The results of treatment are influenced more by such factors as age and pre-existing debilitating disease than by the chemotherapy given (Jensen & Lassen, 1969). Rifampicin could only rarely make a significant difference to the outcome in such cases. With the possible exception of leprosy, it is unjustified to use rifampicin other than in combination with isoniazid or other suitable anti-tuberculosis drug for the treatment of tuberculosis. Its wide spectrum of antibacterial activity, of interest to the bacteriologist, may be best forgotten by the clinician whose direct concern with the treatment of human disease carries with it a responsibility in the use of antibiotics which belongs not only to today but also to tomorrow.

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References