A comparative evaluation of drug combinations used in the treatment of pulmonary tuberculosis

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Summary
A retrospective analysis was undertaken of the hospital records of 185 patients admitted for the first time for treatment of pulmonary tuberculosis. The time to sputum conversion was used to evaluate the efficacy of short-course antituberculosis therapy and to determine the effect of including rifampicin (RMP) in various chemotherapeutic combinations. RMP per se was not found to be a significant variable in the drug combinations studied. The combination of RMP and pyrazinamide, however, showed greater efficacy in achieving earlier sputum conversion. The therapeutic advantage of using these two drugs in combination should be more readily appreciated.

Tuberculosis remains a disease of international significance, particularly in developing countries, where it is associated with high morbidity and mortality. This is reflected in the official 1979 statistics for the RSA (Table 1). Recent advances in the chemotherapy of tuberculosis should result in a dramatic decline in the incidence of the disease. The treatment of tuberculosis, however, is a complex, protracted procedure because of the pathology of the disease, the persistence of causative organisms and the variable, often inadequate, defence of the host. The problems of whom to treat, how many drugs to use and the duration of therapy remain to be resolved.

The incremental value of adding drugs such as rifampicin (RMP) to conventional schedules to reduce treatment time from approximately 12 months to 6 months has been extensively studied in developing and developed countries. In all these investigations the time until sputum conversion occurs, based on direct microscopic examination of sputum smears, has been used as an index of therapeutic response and drug efficacy. Although sputum culture is essential for the definitive diagnosis of tuberculosis, microscopy offers the advantage of speed and lower cost. Transmission of tuberculosis is maintained in the community by subjects whose sputum is so heavily positive that tubercle bacilli can be detected on smear microscopy. Sputum conversion is therefore held to indicate fairly reliably that the individual is no longer infectious.

The present investigation was undertaken to assess: (i) whether the efficacy of short-course chemotherapy for tuberculosis as assessed in terms of sputum conversion time is greater for a drug schedule which includes RMP; and (ii) whether a 4-drug schedule including RMP is more effective than a 3-drug schedule including RMP.

Patients and methods
A retrospective analysis of the hospital records of 185 patients at their first admission for pulmonary tuberculosis was undertaken. The patients had been allocated to the treatment schedules shown in Table II. Sputum conversion time was recorded for each patient. Additional data analysed included age, sex, sputum test grade on culture and drug resistance.

Results
Analysis of the data pertaining to sputum grade and resistance patterns yielded ambiguous results, mainly because of the paucity of data. Analysis of the data pertaining to sputum grade and resistance patterns yielded ambiguous results, mainly because of the paucity of data.

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A comparison between groups 1 and 3 and between groups 1 and 2 (Fig. 1) indicated that a 4-drug schedule including RMP yielded significantly faster sputum conversion rates than the 3-drug schedule including RMP, or the control group \(\chi^2 = 9.5\) and \(\chi^2 = 11.92\) respectively. No differences were found between groups 2 and 3, however, suggesting that RMP per se is not a significant variable. Likewise, the incremental value of a fourth drug (in this case streptomycin) could not be demonstrated. A comparison between groups 1 and 2 and between groups 1 and 4, however, clearly pointed towards the greater efficacy of the combination of RMP and pyrazinamide (PZA), which yielded a significantly shorter sputum conversion time.

These results are essentially in agreement with those found in the British Medical Research Council trials conducted in Hong Kong and Singapore, where combinations of isoniazid (INH), streptomycin, RMP and PZA proved to be most effective.

Interactions of antituberculosis drugs were investigated by Mitchison, who suggested that mycobacterial populations present at any one time in a tuberculosis patient can be differentiated in terms of growth rate, location (intracellular versus extracellular) and oxygen availability.

Synergism may be expected between RMP and PZA because they act on these different bacterial populations. Actively growing organisms in the walls of cavities where the pH is neutral are rapidly killed by INH, RMP and streptomycin. Slowly but continuously growing strains are killed correspondingly more slowly by all these drugs. PZA is active only in an acid pH, and it is therefore active on bacilli which are located inside cells; these are the organisms which are likely to give rise to drug resistance and subsequent therapeutic relapses.

Organisms dormant most of the time but occasionally metabolizing actively for short periods are killed fairly rapidly by RMP; but they do not metabolize long enough for INH and streptomycin to act effectively.

INH kills most of the rapidly growing organisms first, but is relatively inactive against organisms with a slow growth rate. PZA, on the other hand, displays a high degree of activity against this latter group of bacilli.

Conclusions

The significance of the present results lies in the fact that although RMP and PZA are currently used in the treatment of tuberculosis, the particular advantage of their conjoint administration has not been sufficiently appreciated. It is therefore suggested that whenever RMP is prescribed, PZA should be added for maximum effectiveness in achieving early sputum conversion.

Furthermore, the present findings are held to be sufficiently definitive to warrant further research in this area, especially with respect to the effects of the RMP-PZA combination on relapse rates. Further investigation of resistance patterns is also indicated in view of the ambiguous findings encountered during this study. Possibly consideration should be given to the reclassification of PZA as a "first-line drug" in the treatment of tuberculosis.

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Comparison of methohexitone and etomidate for general anaesthesia in unpremedicated outpatients

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Summary

This study compares methohexitone (Brietal; Eli Lilly) and etomidate (Hypnomidate; Janssen) as hypnotic agents for the induction and maintenance of general anaesthesia in outpatients given fentanyl and nitrous oxide for analgesia but no premedication. While both agents provided suitable anaesthesia with a minimal incidence of side-effects, 66% of the patients who received methohexitone were noticeably drowsy 2 hours after the operation, whereas all but 3% of the patients who received etomidate were wide awake.

The ideal general anaesthetic for outpatients requiring short surgical procedures without premedication should be safe and reliable, and rapidly induce anaesthesia with subsequent adequate hypnosis and analgesia. This should be followed by rapid recovery to full consciousness, permitting early discharge of the patient. There should be a minimum of unpleasant side-effects such as pain on injection, involuntary muscle movements, postoperative nausea or hallucinations. These requirements are difficult to meet, and many varied techniques are advocated. As there is no single agent available which fulfils all these demands satisfactorily, it is necessary to combine one of the more appropriate intravenous induction agents with an analgesic agent such as nitrous oxide (N₂O) and/or fentanyl, which also allows rapid recovery. It would appear from the literature that the induction agent most suitable in this situation, provided there are no contraindications to its use, is methohexitone (Brietal; Eli Lilly). An alternative agent is etomidate (Hypnomidate; Janssen), a rapidly metabolized eugenol derivative with similar unpleasant side-effects to those of methohexitone (i.e. pain on injection and involuntary muscle movements).³⁴

Methohexitone and etomidate have already been compared as induction agents for general anaesthesia in premedicated patients.⁵ Recently it has been found that the use of fentanyl intravenously reduces the pain on injection and the involuntary muscle movements associated with etomidate.⁶ This study compares methohexitone and etomidate as hypnotic agents for the induction and maintenance of general anaesthesia in unpremedicated outpatients given fentanyl and N₂O for analgesia.

Patients and methods

Fifty-seven female patients scheduled for consecutive minor (outpatient-type) gynaecological procedures in a busy gynaecological theatre were included in the study. All the patients were of physical status group I or II according to American Society of Anaesthesists’ (ASA) standards. None of the patients was seen pre-operatively by either of the two investigators present on each day, but all were assessed as regards fitness for general anaesthesia by an independent clinician. All patients were weighed pre-operatively and their age, ASA group, pulse rate and blood pressure recorded. On arrival in the operating room each patient was prepared for non-invasive monitoring of the peripheral pulse rate, systolic blood pressure, ECG and expired tidal volume. An intravenous line was established on the dorsum of the hand or distal forearm. When the patient had relaxed, baseline pulse rate, blood pressure, ECG and tidal volume were recorded. All patients were then given N₂O 66% (4 l/min) and O₂.