

PAST DEVELOPMENT, PRESENT STATUS AND FUTURE PROSPECTS OF COMBINED CHEMOTHERAPY OF HUMAN TUBERCULOSIS

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Summary: While search for an ideal drug continues, use of available drugs should be optimised. The object of multiple drug combinations is not merely to prevent the selection of resistant mutants but also to ensure bactericidal action in respect of various subgroups of the bacillary population of a lesion in respect of their metabolic and growth characteristics. Pharmacokinetic studies have shown that the drugs do not interfere with each other's action and all the three oral bactericidal drugs can be administered in a single preparation, thus reducing the number of pills/capsules to be swallowed by the patient and the possibility of the patient omitting one or the other drug inadvertently. SM, INH, RMP and PZA reach their peak concentration approximately 2 hours after administration, the peak being 20-30 meg/ml in the case of SM and PZA and 10-12 meg/ml for RMP and INH. There are, however, marked inter-individual and intra-individual variations in absorption and excretion of drugs and their effectiveness is related more to the height of the peak blood levels achieved than their half-life.

In his book entitled "Pulmonary tuberculosis, a journey down the Centuries" (I), R.Y. Keers writes: Those of us whose acquaintance with tuberculosis began in the early 1930s have witnessed a wonderful metamorphosis and now that it has become possible to speak of the cure of tuberculosis without putting the word cure in inverted commas we may be forgiven if we believe in our hearts that the discovery of anti-tuberculosis chemotherapy constituted the greatest medical miracle of the twentieth century".

All those who have been and are involved in antituberculous chemotherapy, will certainly regard such a statement with a justified sense of gratification. The medical progress towards the control of the disease has, in fact, been remarkable over the last few decades to such an extent that the future eradication of the disease depends more on the solution of socio-economical than of purely medical problems. In antituberculous chemotherapy two parameters have shown a major decrease as a result of research, namely the duration of treatment and the number of doses of drugs needed to achieve a satisfactory treatment. The former has come down from the 18-24 months of the conventional isoniazid-streptomycin-PAS regimen to the present 9-6 months, the latter from more than 2000 doses to less than 100. The positive impact in terms of patient's compliance is evident. With the conventional regimens, the prospect of a long-lasting treatment led a substantial proportion of patients to abscond from treatment as soon as they started feeling better, a fact which had a negative effect in epidemiological terms since many such patients absconded from treatment when still harbouring bacilli in their bronchial secretion. The present attitude of administering in the initial intensive phase of treatment a combi-

nation of 4 potent bactericidal drugs, in addition to leading to a rapid sterilization of the individual patient must be regarded as a preventive measure for potential absconders to infect further individuals in their community.

As is well known, the combination of several drugs in a disease like tuberculosis characterized by high homogeneous bacterial inocula in relatively small areas (caverns) is aimed at preventing the selection of resistant mutants to one or more of the drugs used. For every chemotherapeutic agent it is in fact possible to estimate the genetic mutation rate towards resistant for a given bacterial species. For *M. tuberculosis* the mutation rate is of the order of 1×10^{-5} for isoniazid and streptomycin, of 1×10^{-8} for rifampicin, of 1×10^{-3} for pyrazinamide and thioacetazone.

This means that a population of 100,000,000 of bacilli (10^8) contains one bacterium resistant to rifampicin, 1000 bacteria resistant to isoniazid and streptomycin, 100,000 bacteria resistant to pyrazinamide and so on. We also know that the possibility of finding a bacterium *simultaneously* resistant to a given number of drugs and therefore capable of escaping the killing, is given by the product of the individual mutation rates and is calculated by summing the exponents. It is therefore clear that it will be exceedingly difficult to find a patient with such an enormous bacterial population to contain one bacterium simultaneously resistant to the four drugs used today in the initial intensive phase. The correctness of this approach is confirmed by the clinical results obtained in some carefully conducted clinical trials. Bacteriological failures, when occurring, are almost invariably with bacilli fully sensitive to the drugs employed. Retreatment can therefore be with the same drugs, without the need for

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resorting to other compounds. The therapeutic value of the drugs is therefore maintained over the time emphasizing the importance of multi drug-chemotherapy, which should always be applied without exceptions. Another positive aspect of the present antituberculous regimens is represented by their effectiveness in presence of both a fully sensitive initial bacterial population or a partially sensitive one. This is of particular value for developing countries where initial resistance to isoniazid, to streptomycin or to both drugs is relatively frequent. This finding results in making initial sensitivity testing unnecessary with a noticeable reduction in operational expenses particularly in large-scale programmes.

Of the 4 drugs used, streptomycin, isoniazid and pyrazinamide are relatively old compounds having been developed in the fifties; rifampicin is relatively new. The obvious equation, long life of a drug-better knowledge, is not always true. It looks as if the more a drug is established in its therapeutic use the less it seems to attract the attention of the investigators. Studies on the absorption, metabolism and excretion of the older drugs are non-systematic and relatively rare so that their dosage, for example, is based more on the integration on very practical ground, of such parameters as dosage-clinical effect-toxicity than on specific studies. As a result, streptomycin is generally used at the daily dose of 1g, i.m., isoniazid at approximately 5 mg/ Kg body weight although ample deviations from this dosage were present only a few years ago, both in adults and in children. For pyrazinamide the main factor affecting the prescribing habits of the clinicians has been its hepatotoxicity. The drug, used at the daily dose of 5-6 grams gave rise to a series of cases of liver side effects which almost led to its abandonment from clinical use. The availability of rifampicin and the combination with other bactericidal agents such as isoniazid and streptomycin made it possible to reduce the dosage of pyrazinamide to a level where the relationship efficacy/toxicity was acceptable. In general, the selection and dosage of the drugs to be combined has been performed on very practical clinical data, in absence of a rationale based on specific studies.

Only very recently a hypothesis on specific bacterial targets for each drug employed has been put forward (2). The bacillary population of a cavern has been in fact divided in 4 sub-groups each with specific metabolic and growth characteristics. We now know that, apart from the prevention of resistance aspect, drugs can be combined on the basis of their capacity of attacking a definite bacterial sub-groups. Streptomycin, isoniazid and rifampicin kill actively growing bacilli, rifampicin seems

to be particularly suitable for killing intermittently growing bacilli. Pyrazinamide (with its metabolic derivative pyrazinoic-acid) and rifampicin are capable of penetrating macrophages and retain their microbiological activity at acid pH. No compound is known to act on metabolically inactive (dormant) bacilli.

As stated above, very few data were available on the pharmacokinetics of antituberculous drugs not only individually but also when given in combination. In the past, a study had been carried out on the combination of rifampicin and isoniazid, particularly useful as a pharmacokinetic basis for the 9-months double-drug regimens (3). To satisfy this need a study has been performed with the aim of assessing the pharmacokinetic parameters of the 4 drugs used in the initial intensive phase given once alone and once in free combination. The results of this study have indicated that similar data on absorption and metabolism were observed after individual and combined administration. The drugs did not interfere with each other in pharmacokinetic terms. In the plasma, the 4 drugs reach their peak concentrations at approximately 2 hours after dosing. The levels of streptomycin and pyrazinamide range between 20 and 30 meg/ml whereas those of isoniazid and rifampicin range between 10 and 12 meg/ml. The time-course of the main metabolites of isoniazid, rifampicin and pyrazinamide, namely acetyl-isoniazid, desacetyl-rifampicin and pyrazinoic-acid were also similar suggesting no metabolic interference between drugs.

As mentioned in the introduction, the present regimens of short duration have proven their outstanding efficacy in strictly controlled experimental conditions. Their potential effectiveness in large-scale campaigns could be reduced by several factors, one of them being the relative complexity of the drug-delivery process owing to the still high number of drugs to be given, particularly in the initial intensive phase, the difficulties inherent in the process of adjustment of the number of the pills to the varying body weight of the patients etc. A not secondary limiting factor could also be represented by unforeseen shortage of one or more of the drugs during treatment. Finally, in both daily and intermittent regimens, the high number of medications to be ingested could result in a relatively high number of patients exhibiting G.I. side effects resulting in turn in poor overall compliance on the part of the patients.

As a possible way of overcoming these limiting factors we thought it worth while to study a preparation containing the 3 oral drugs, isoniazid, rifampicin and pyrazinamide in such a ratio as to make it possible to match the mg/Kg

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needs of each individual drug through an adjustment of the number of the pills in function of the patients' body weight.

As a basis for developing such a triple combination tablet an analysis was carried out on the international literature to establish the actual dosage of the 3 drugs. Not surprisingly, the attitude of pre-establishing the daily dose of each drug in patients whose body weight can vary quite remarkably, results in corresponding deviations of the actually administered mg/Kg dose from that stated in the various papers as having been given. In a large sample of clinical trial reports it was possible to establish that isoniazid is administered at a dosage which ranges from -7% to +70% of the allegedly administered amount of 5 mg/Kg b.w., rifampicin from -8% to +25% and pyrazinamide from +20% to +40%.

In spite of such remarkable deviations, the clinical results were uniformly satisfactory suggesting that with the present regimens the accuracy of treatment plays a much greater role in making a successful treatment than alterations in drug dosage. In a particular study carried out in South Africa the range of "active" dosage was from 13.3 to 25.0 mg/Kg for streptomycin, from 4.0 to 7.5 mg/Kg for isoniazid, from 8.0 to 15.0 mg/Kg for rifampicin and from 27.0 to 50 mg/Kg for pyrazinamide(4).

These data are of particular interest since they have been obtained in a country where the majority of the population is thought to belong to the fast acetylator of isoniazid type, a fact which led some investigators and clinicians to claim that the daily dosage of isoniazid should always exceed 8 mg/Kg.

These findings seem to support the hypothesis that with bactericidal drugs like isoniazid, effectiveness is more related to the height of the peaks in blood than to the persistence of the drug in the blood as estimated by the rate of disappearance from this compartment (half-life). We should therefore stop talking of definite mg/Kg dosage and refer more appropriately to a range of active mg/Kg doses. We have also to take into account the basic pharmacokinetic principle of the between-subjects and within-subjects variations in absorption and excretion. In the study I was referring to before, it was found that serum level curves characterized by important difference in pharmacokinetic parameters were found in patients treated with the same mg/Kg dose.

In some cases peak concentrations were inversely correlated with the administered dose so that higher levels were achieved in patients receiving a lower dose than in other patients receiving a higher one. This is a common situation with antibiotics administered through the oral route and where the liver first pass effect can affect to an unpredictable degree the time course of the serum levels and tissue distribution. Within these limits the study in which the absorption and excretion of rifampicin, isoniazid and pyrazinamide given in combined-individual administration was compared to that of the fixed-triple combination indicated the lack of any pharmacokinetic interference between the 3 drugs. These results seem most encouraging in view of a possible simplification of the multiple-drug regimens.

Research in tuberculosis is going on in laboratories, clinics and institutions all over the world. It is highly probable that new and interesting remedies will be made available to the therapeutic community in not too distant a future.

It would be a mistake, however, not to take immediate advantage of what the research has made available now. Optimizing the use of the available drug regimens as well as any other appropriate resource is first duty of all people involved in the fight against tuberculosis. Lassitude and lack of creativity and aggressiveness now could prove to be disastrous in the future. The success achieved in the technically advanced countries could be more than counterbalanced by the increase in population at risk in the developing countries, and make such a success globally useless.

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