Combined Antimicrobial Therapy

edited by
W. Brumfitt, L. Curcio and
L. Silvestri

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Combined antimicrobial therapy

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Foreword

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Ladies and Gentlemen,

I believe that the best way of fulfilling the assignment given to me for this workshop is to explain why the Organizing Committee has chosen the subject of combined therapy.

The main reason for this choice has been the knowledge that many problems in the field of combined chemotherapy — about which specialists have conflicting ideas — still remain to be solved. A typical example of this situation is tuberculosis, which is treated by compulsory combined therapy. A physician prescribing a monotherapy would be criticized by all his colleagues. Meanwhile, outside the field of tuberculosis, many specialists consider monotherapy to be the ideal treatment for infectious diseases.

On the basis of these premises, the Organizing Committee has ignored the traditional barriers among disciplines and invited to this workshop both specialists in anti-tubercular therapy and specialists in infectious diseases. Furthermore, experts in antitumoral therapy have been invited, even though tumours are not infectious diseases. This is because striking analogies do in fact exist, chiefly with regard to the problem of drug resistance, which the investigators hope to control by means of combined therapy.

If the investigators assembled here succeed in making an important contribution, even if not providing a definitive answer, to the question of whether true biological and medical reasons exist to explain the differences between these two therapeutic approaches, then our workshop will not have failed.

One of the principal aims of combined therapy is to control the emergence of resistant strains. Nevertheless, ideas on resistant strains differ. According to some investigators, the diffusion of resistant strains constitutes a considerable potential danger, chiefly when seen

in perspective. Other researchers feel that this danger has been exaggerated. They feel that the therapeutic agents available to date and in the future constitute a considerable force and that it will always be possible, among so many drugs, to find an agent that will maintain its efficacy. The opinion of these investigators is that the reduction of the use of antibiotics which show a decrease in efficacy, will cause the disappearance of the resistant strains, which will no longer be exposed to selective pressure, whilst the microbial population will recover its original sensitivity.

On the other hand, some investigators feel that the current practice which recommends monotherapy might be the principal if not the only cause of the diffusion of resistant strains. As has been demonstrated, the frequency of resistance reflects the frequency with which an antibiotic is employed.

There is another aspect of resistance which is worthy of discussion. In long course diseases, e.g. tuberculosis or some chronic urinary tract infections, the failure of therapy is determined by the selection of resistant mutants. On the other hand the treatment of an acute infectious disease may fail, on rare occasions, because of the selection of resistant mutants during treatment. In this type of diseases failures are generally due to treatment being started too late, when the lesions induced by bacterial proliferation are no longer reversible, whilst the natural host defences are no longer sufficient. It is to be presumed that during monotherapy there is always an increase in resistant strains controlled by the natural host defences.

It is likely that in the case of cure of the patient, the diffusion of resistant strains depends upon the diffusion into the environment of resistant bacteria during monotherapeutic treatments, even when these are successful.

If all these hypotheses are true, when comparing monotherapy to combined therapy we should take into consideration not only the advantages to individual patients, but also the epidemiological consequences, and the pressure which the different therapies exert on the evolution of microbial populations towards resistance.

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1

The epidemiological study of enterobacteria carrying resistance plasmids

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Summary

The indiscriminate use of antibacterial drugs throughout the world has resulted in the emergence of multiresistant strains of important enterobacterial pathogens such as Shiga's bacillus and *Salmonella typhi* which have caused extensive and serious epidemics of the respective diseases. Multiresistant strains of *S. typhimurium* have also caused widespread and severe epidemics, predominantly in children. These outbreaks, which have high morbidity and mortality rates, may involve a number of countries. The bacterial strains concerned seem to be cycling in man, and the epidemics are clonal in origin. The epidemiology is at present obscure, except when the strains gain entry to hospitals, where nosocomial spread is rapid.

The multiresistant strains responsible for these outbreaks may have acquired unidentified plasmids coding for communicability and virulence.

Introduction

Combined antimicrobial therapy, in the sense that it involves the use of more than one antibiotic or synthetic antimicrobial drug (all will be called antibiotics hereafter) is of two sorts: the employment of two different antibiotics marketed in a fixed ratio mixture; and the use of multiple antibiotics, simultaneously or sequentially. The first use is in general regarded unfavourably nowadays, with the exception of cotrimoxazole, a mixture of sulphamethoxazole and trimethoprim. The use of separate multiple antibiotics is only too frequently the result of lack of response to the first drug(s) administered, in illnesses that may not be diagnosed beyond the point of their being febrile. The sequence may even involve changes of drug, in the event of apparent lack of response to each antibiotic in

turn, until the infection finally subsides. The tendency is then to attribute cure of the illness to the last antibiotic employed. In fact, such resolution is usually the result of the infection having run its course, the end of which coincides with the last antibiotic administered. Many of these illnesses are viral in origin, and are untouched by antibiotics. And a high proportion of the patients are children, who are running the gauntlet of viral infections that contribute to the immunity of the adult. Antibiotics have even been used for routine prophylaxis in all children admitted to some hospitals, a nefarious practice that should be totally abandoned.

Of course, the doctor-patient relationship has been radically changed by the fact that everyone now knows about the wonder-drugs. And if a doctor has not used one of them within 24 hours of seeing a febrile patient - frequently a child - his professional competence is doubted, whether or not the ailment has been diagnosed. There is therefore heavy social pressure on the general practitioner to use antibiotics from the start, and as I have already indicated, if there is no apparent response within a day or two, he is tempted to change to another antibiotic. The same lack of therapeutic prudence also occurs in many hospitals.

I was a general practitioner in the 1930s, and I treated many patients with febrile illnesses. Children with viral diseases of then unknown aetiology usually recovered within three to five days. Treatment was symptomatic: there was no more specific therapy for these illnesses then than there is now. Yet we did not become alarmed about the persistence of fever for a few days, because experience had taught us that in the great majority of cases it would subside within a week. There were, of course, the specifically identifiable febrile diseases, such as streptococcal infections. for which we had no remedy until the introduction of the sulphonamides, an event that happened while I was in general practice. But an experienced eye could diagnose a streptococcal throat at a glance, and throat swabs were routinely taken for confirmation. Unfortunately, the indiscriminate use of sulphonamides soon limited their effectiveness, though they remain valuable drugs to this day.

Influenza was another recognisable disease, but it had to run its course, and we did not panic if the pyrexia lasted as long as a week, because most cases resolved uneventfully. We still have no effective drug for it, but prophylactic vaccination shows promising results.

The point I am making is that it was recognised at that time that the great bulk of febrile infections abated without the use of drugs, except perhaps where they were indicated on symptomatic grounds. We knew that most febrile infections resolved spontaneously, and we were not alarmed when they took a few days to do so.

The picture is very different today, when there seems to be a

general impression that patients with persistent fever are at serious risk if antibiotics are not used: if the doctors do not have that impression the patients'relatives have, so the doctor is under heavy pressure to use antibiotics, whether he is convinced they are necessary or not. This pressure has added an important dimension to current medical practice.

Risks of combined chemotherapy

There are several risks involved in combined chemotherapy.

1. The action of the drugs may be such that one is rendered ineffective by the use of the other. For example, the penicillins act on exponentially growing bacteria, while chloramphenicol is bacteriostatic. It is therefore illogical to use these drugs together.
2. Antibiotics used together in a fixed ratio may be no more effective than each antibiotic used separately, and in any event, even if their results are additive or synergistic, the ratio in which they are combined may not be optimal.
3. The combined antibiotics may present more risk of adverse reactions than the respective antibiotics used alone.
4. The use of any antibiotic may result in the appearance of bacteria with chromosomally determined or plasmid-mediated drug resistance. The risk of multiple drug resistance increases with the multiplicity of antibiotics. Combined chemotherapy thus adds to the risk of the emergence of multiply resistant bacteria.

To this catalogue can be added the fact that the use of antibiotics for the therapy of infections caused by resistant bacteria favours the respective pathogens while inhibiting sensitive competing bacteria, so that in such instances the antibiotics will not only be useless against the infections, but may actually promote them. Moreover, when infection is caused by bacteria with multiple resistance, the use of any antibiotic represented in the spectrum of resistance will select for the organism with all the resistances - a serious matter when that spectrum may extend to as many as nine resistances.

Having set the stage for a number of cautionary tales relating to bacterial drug resistance - I am confining myself to the enterobacteria - I think it worth while to describe the first clearly defined major instance in which the indiscriminate use of antibiotics led to a prolonged outbreak of multiply drug-resistant bacteria in animals and man, caused by phage-type 29 of *S. typhimurium* [1], [2], [3].

Type 29 of *S. typhimurium* was first described by Callow [4]. Its incidence was low until the winter of 1963-1964, when it suddenly increased. After a short pause in 1964, it resumed its upward trend,