PROFESSOR ANTHONY COATES ON HOW THE COMBINATION OF TWO ANTIBIOTICS RESULTS IN SYNERGISM AND ADDITIONAL BENEFITS, SUCH AS REDUCING THE EMERGENCE OF RESISTANCE

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In my previous Pan European Networks articles, I have suggested that the research and development of new antibiotics should be boosted in the following ways: the European Commission should set up an antibiotic recovery programme, which would deliver loans and grants to SMEs, large pharmaceutical companies and universities. This programme should aim to provide the world with 20 new classes of antibiotics. In addition, the guidelines which are implemented by the regulators should be adapted to cope with the increased need for novel antibiotics, for example by widening the number of clinical indications for which microbiological endpoints are allowed for marketing purposes. Moreover, I have suggested that the UK and other countries should set up collaborative networks, at the national and international level, of universities and pharmaceutical companies which would aim to rebuild the infrastructure of antibiotic discovery.

In this article, I address the role of combinations of antibiotics in the treatment of antibiotic resistant bacterial infections. In this context, at least one drug in the combination would be a new compound.

Successful combinations

1. Prevent resistance

The first, and most successful, antibiotic combination was the addition of a second drug to streptomycin in the 1950s to prevent the emergence of resistance in tuberculosis patients during treatment. Modern therapy of tuberculosis is based upon these principles which were developed by Denny Mitchison and his colleagues. Using a combination of drugs to prevent resistance was extended to the treatment of leprosy, AIDS and cancer, and it is important to realise that the success of tuberculosis combination therapy is dependent on the fact that the causative agent, *Mycobacterium tuberculosis,* becomes resistant to antibiotics by chromosomal mutations.

2. Synergy

Combinations are used in order to enhance the action of one antibiotic by another. For example, the combination of penicillin and gentamicin for the treatment of endocarditis with organisms which are sensitive to both antibiotics. Such combinations are synergistic.

3. Target resistance

Combinations have been developed which will enhance the activity of an antibiotic against resistant bacteria. An example of this approach is the combination of amoxicillin with the bacterial beta-lactamase inhibitor clavulanic acid. This combination has been shown to be superior to amoxicillin alone in the treatment of impetigo.

4. Shorten regimens

Combinations can target dormant subpopulations. This can shorten regimens, for instance in tuberculosis where the addition of rifampicin and pyrazinamide reduce the duration of treatment from 18 months to six months.

Patient compliance with the combination is crucial. Low compliance, in other words poor adherence to the regimen, is associated with the emergence of resistance. In tuberculosis, where the treatment regimen lasts for six months, shortening the course of drugs is a priority for drug development in order to increase patient adherence to the regimen.

5. Widen the spectrum of bacteria which are targeted

Broadening of the species of bacteria which are killed is also important. For instance, in acutely sick patients with sepsis, the responsible bacterial species may not be known initially. Accordingly, doctors often treat such patients with a combination of a beta-lactam and an aminoglycoside. When the blood culture results are known, more specific antibiotic therapy can be introduced, but if multiple different species are thought to be the cause of the infection, the combination may be continued.

Ideal characteristics

In my view, the partner drug should target the bacterial cell membrane rather than a single enzyme. This would reduce the likelihood of induction of resistance. It should avoid exposure to the gut bacterial flora, where it is likely to induce resistance. The combination regimen should be short in order to increase patient compliance and reduce the risk of emergence of resistance.

The ideal second partner would be synergistic and active against dormant bacteria, thus potentially reducing the duration of therapy and be able to kill a wide range of resistant mutants which arise during therapy to the old antibiotic which is its partner.

The partner drug should also be able to enhance the efficacy of the old antibiotic against sensitive and resistant bacteria, and should be active against dormant bacterial subpopulations which may help to reduce the emergence of resistance. In addition, it should broaden the number of species which the old antibiotic kills.

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