

is likely to be synergistic, indifferent, or antagonistic. Furthermore, clinical studies purporting to confirm laboratory synergism were poorly conducted and controlled, and provided no real evidence that fixed combinations were more effective than when either of the antimicrobial agents was used alone.

Another reason advanced for the use of fixed combinations is that they are likely to be effective in infections caused by a mixture of bacteria, some of which are susceptible to one of the antibiotics and the rest to the other. In actual practice, however, one organism is usually chiefly responsible for clinical infections and the best results are obtained by concentrating on this major pathogen. In the instances where a second antibiotic is likely to be helpful, it is best to obtain cultures and to determine the susceptibility of the micro-organisms to a number of antibiotics. Clinical studies demonstrating the superiority of fixed combinations in infections involving mixtures of bacteria are not available.

Delaying the emergence of antibiotic-resistant bacteria is still another reason given for prescribing antibiotic combinations, but there is no substantial evidence that this objective has been accomplished by the fixed combinations now on the market. Rather, the evidence indicates that bacteria are likely to become resistant to both of the antibacterial agents present in the combination. Finally, by broadening the spectrum of bacteria affected, fixed combinations are frequently administered to increase the likelihood of providing effective therapy. However, in the infections where fixed combinations are commonly used it has not been proven by clinical comparisons that the results are better than when one of the antibiotics is given alone. In seriously ill patients where the infecting organism has not yet been determined, it is indeed proper to administer more than one antibiotic. When this is done, each antibiotic should be selected carefully on the basis of the most likely diagnosis, and they should be administered separately, with dosages being adjusted according to the patient's needs. This involves assessing many factors, including the function of vital organs such as the liver and kidneys.

Thus, aside from the fact that fixed combinations have not been proven to have therapeutic advantages, their use means that the patient is unnecessarily exposed to the toxicity and side effects of two antibiotics rather than one, there is a lack of flexibility of dosage of the individual components, and the development of resistance of bacteria to a number of antibiotics is encouraged.

It might be enlightening now to describe one of the more widely used fixed combinations in relation to the problem of efficacy. Panalba is a fixed combination of two antibiotics, tetracycline and novobiocin. Tetracycline is a first-line antibiotic with a wide spectrum of activity that has been used successfully as a single entity in a great variety of infections for over 15 years. Novobiocin has a fairly narrow range of activity, bacteria quickly become resistant to it, and it has a predilection for causing skin rashes and other side effects. Novobiocin was marketed as a single drug for a few years by Merck, who then dropped it because of its undesirable characteristics and a lack of wide acceptance. Upjohn, with access to both tetracycline and novobiocin, mixed them in the same capsule and has marketed this fixed combination under the trade name of Panalba for a number of years.