TRIMETHOPRIM AND RIFAMPICIN IN COMBINATION AGAINST *ESCHERICHIA COLI*

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In vitro, trimethoprim (Tp) has been shown to act synergistically with sulfamethoxazole (Sx) against *E. coli* (Bushby and Hitchings 1968). However, when these two drugs were used in combination under similar conditions to those found in vivo, there was a negligible co-operative effect between them (Amyes and Dible 1979). Rifampicin (Rif) is an antitubercle drug, but it has been reported that if it is used in combination with Tp against common pathogens the effect can be synergistic (Kerry, Hamilton-Miller and Brumfitt 1975) and hence Rif may be a suitable candidate to replace Sx. However, it has also been reported that this combination can actually be antagonistic (Harvey 1978). This communication investigates this paradox by examining the effect of these two drugs on *E. coli* under conditions similar to those found in urine.

The interaction between Rif and Tp was measured against sensitive, Tp-resistant Sx-resistant and Rif-resistant derivatives of *E. coli* K_{12}. The fractional inhibitory index for Tp and Rif was determined on solid DM medium (Amyes 1978). The sensitive strain exhibited synergy by this method while the three types of resistant bacteria exhibited only additive effects. Logarithmic phase cultures of the sensitive *E. coli* K_{12} were subcultured into DM medium and the viability followed. In the presence of methionine, glycine and adenine, only at limiting concentrations did Tp and Rif cause a bactericidal response when used in combination and a bacteriostatic response when each drug was used singly at these concentrations. A similar response was found with Sx-resistant strains. When strains containing R-plasmids conferring Tp resistance were tested there was no synergy observed when Tp and Rif were used in combination. Similarly, when the experiment was repeated with a Rif-resistant mutant, the mixture of the two drugs failed to exhibit synergy.

The mutational frequencies of Tp-sensitive and Tp-resistant bacteria to rifampicin resistance were examined to determine whether the presence of Tp and Rif together may delay the emergence of Rif-resistant bacteria. The sensitive organism exhibited a mutational frequency to Rif-resistance at a rate of 2×10^{-7}. The mutation was not detectable when Tp was added. The mutational frequencies to Rif-resistance in the Tp-resistant strains were the same in the presence and absence of Tp. The effect of the combination on the transfer of Tp R-plasmids was examined. Surprisingly, Rif-resistant mutants were better donors of R-plasmids than their sensitive counterparts and slightly less efficient as recipients. Therefore, the development of Rif-resistance in harbouring R-factors conferring Tp-resistance may actually promote the transfer of resistance rather than decrease it.

The results show that there is no obvious advantage in combining Tp with Rif in the treatment of *E. coli* infections. Although Rif would be able to inhibit Tp-resistant strains, mutation to Rif-resistance is rapid and, once established, may even promote the transfer of Tp R-plasmids to other Tp-sensitive bacteria.

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