CO-TRIMOXAZOLE SYNERGY IN SENSITIVE AND RESISTANT BACTERIA

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The synergy between trimethoprim (Tm) and sulphamethoxazole (Sx) occurs with bacteria that are sensitive to both drugs and with some bacteria that possess plasmids which confer resistance to one of the two drugs. This phenomenon is most easily demonstrated using the agar diffusion technique with separate antimicrobial disks (Amyes, 1978) or by determining the fractional inhibitory concentration using an isobologram (Elion, Singer & Hitchings, 1954). However, both these methods measure only the bacteriostatic effects of the combination. It was originally proposed that the combination promotes a bactericidal effect (Bushby & Hitchings, 1968) and so the viability of derivatives of Escherichia coli K_{12} were examined in the presence of both drugs.

When E. coli K_{12} was subcultured into Davis-Mingioli minimal medium (Davis & Mingioli, 1950) containing both drugs, there was no loss of viability. This is similar to the results found with the individual drugs (Amyes & Smith, 1974; Angehrn & Then, 1973). However, Tm is able to produce a rapid bactericidal effect by itself in minimal medium containing vitamin-free casamino acids and adenine (Amyes & Smith, 1974). The concentration of Tm required to give the maximum bactericidal effect was 0.4µg/ml or more whereas no inhibition of growth was observed with 0.04µg/ml or less. When Sx was additionally present, at 20 times the Tm concentration, a loss of viability was observed in cultures with 0.04µg/ml Tm whereas none was found with 0.02µg/ml Tm. The potentiation of Tm action by Sx occurred only between 0.04 and 0.2µg/ml Tm. The concentration of Sx was also critical as no bactericidal response was seen with a Tm:Sx ratio of less than 1:10 and no further bactericidal response was seen with a ratio of greater than 1:20.

Similar experiments were performed with E. coli K_{12} harbouring the sulphonamide resistance plasmids R1 and SSu. Both strains grew well in the presence of 1000µg/ml Sx and gave the same response to Tm as the sensitive strain. When E. coli K_{12} (R1) was treated with 0.04µg/ml Tm and 0.8µg/ml Sx, there was a loss of viability which was increased by raising the sulphonamide concentration. No concentration of Sx could potentiate trimethoprim with E. coli K_{12} (SSu).

Two trimethoprim resistance plasmids were tested in E. coli K_{12}. The plasmids R751 and R483, allow their hosts to grow uninhibited in medium containing 1000µg/ml Tm. The presence of 100µg/ml Sx gives a normal bacteriostatic effect. However if Tm was additionally present at relatively low concentrations, there was a loss of viability with E. coli K_{12} (R751) that did not occur with E. coli K_{12} (R483).

The synergy between trimethoprim and sulphamethoxazole in sensitive bacteria is to increase, in effect, the trimethoprim concentration. However, this only occurs under specific conditions over a very narrow range of trimethoprim concentrations. On the other hand, in some bacteria resistant to one of these drugs the role of synergy is more important.

We wish to thank the Scottish Home and Health Department for their financial support of this work.

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