Isolation of Trimethoprim-Resistant, Sulfonamide-Susceptible Enterobacteriaceae from Urinary Tract Infections

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The isolation of trimethoprim-resistant, sulfonamide-susceptible Enterobacteriaceae causing urinary tract infections is reported. The appearance of these strains followed the introduction of trimethoprim alone for use as treatment. Trimethoprim resistance was attributable to plasmids or transposons less frequently in sulfonamide-susceptible Escherichia coli isolates than in sulfonamide-resistant strains.

Trimethoprim in combination with sulfamethoxazole (co-trimoxazole) has been widely used in England since 1969, after which it became generally available as a single drug for the treatment of urinary tract infections in October 1979. A number of different forms of trimethoprim resistance have been reported (1, 2, 6, 8), and there has been much speculation and discussion about the possible effects on the incidence of trimethoprim-resistant bacteria resulting from the release of trimethoprim alone for use as treatment. Since 1978 we have studied the incidence of trimethoprim resistance in Enterobacteriaceae in both hospitals and the general environment (5). In this paper, we report on the recent emergence of bacterial isolates resistant to trimethoprim but susceptible to sulfonamides.

During the survey periods of January through June 1978 through 1982, enterobacteria isolated from infected urine specimens (≥10^3 organisms per ml) received in our diagnostic laboratory were identified by standard laboratory techniques and tested for resistance to trimethoprim and sulfamethoxazole by using multipoint inoculation (with a final inoculum of ca. 100 CFU) onto plates of Oxoid diagnostic sensitivity test agar containing 4% (vol/vol) lysed horse blood plus doubling dilutions of antibiotic. Repeat specimens from the same patient were excluded. The data in Table 1 show the total number of strains examined, the percentage which were resistant to ≥8 μg of trimethoprim lactate per ml, and the percentage of the trimethoprim-resistant strains which were susceptible to ≤16 μg of sulfamethoxazole per ml. All of the strains grew on lysed blood medium used for susceptibility testing; therefore, none of these resistant isolates required thymine for growth (2). The amount of trimethoprim resistance increased over the survey periods for isolates from both hospitals and patients of general practitioners. Some fluctuations were observed, however, particularly in hospital strains of Klebsiella spp., an observation which might reflect the degrees of success or failure achieved in controlling the spread of particular resistant organisms among hospitalized patients. The initial appearance of trimethoprim-resistant, sulfonamide-susceptible strains occurred in 1980 (i.e., after the introduction of trimethoprim alone for use as treatment), and by 1982, such strains accounted for ca. 10 to 15% of the total trimethoprim-resistant strains isolated in our laboratory.

The genetic mechanisms of trimethoprim resistance in E. coli have been widely studied, and we were therefore interested in determining whether any particular type of trimethoprim resistance was predominant among sulfonamide-susceptible E. coli strains. Accordingly, this group of strains (77 separate isolates) was tested for (i) the ability to transfer trimethoprim resistance to a standard E. coli K-12 recipient (7), (ii) the presence of non-autotransferring trimethoprim resistance plasmids (8), and (iii) the presence of trimethoprim resistance transposons in the absence of a detectable plasmid (8). Strains not belonging to one of these three categories were considered to carry chromosomal mutations to trimethoprim resistance (3, 4). A similar analysis of trimethoprim-resistant, sulfonamide-resistant strains (328 separate isolates) isolated during the 1981 survey period was also carried out. The data in Table 2 show the percentage of each group of strains which belonged to the various categories, although it should be noted that the sulfonamide-susceptible group was isolated over a longer time span than was the

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sulfonamide-resistant group. Bearing this qualification in mind, we found that the most notable difference between the two groups was that the proportion of isolates which owed their trimethoprim resistance to plasmids or transposons was lower in the sulfonamide-susceptible group than in the sulfonamide-resistant group. As it seems highly unlikely that the sulfonamide-susceptible group could have been selected for by the use of co-trimoxazole, it is possible that the use of trimethoprim alone resulted in enhanced selection of chromosomal mutations to trimethoprim resistance.

Our results provide evidence for the changed selection pressures resulting from the introduction of trimethoprim alone for treatment of urinary tract infections in the United Kingdom. As yet, the proportion of trimethoprim-resistant isolates which are sulfonamide susceptible remains fairly low. The results in Table 1, obtained over a 5-year period, suggest that the rate of increase of trimethoprim resistance may be lessening. If this is the case, it seems possible that any further increase in the overall level of trimethoprim resistance could result from the appearance of resistant organisms (by either mutation or the spread of preexisting trimethoprim resistance plasmids and transposons) in that proportion of the bacterial population which was previously susceptible to sulfonamides.

**LITERATURE CITED**


