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HIGH INCIDENCE OF CEFUROXIME RESISTANCE AMONG *SALMONELLAE* STRAINS RESPONSIBLE FOR GASTROINTESTINAL INFECTIONS

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During an intensive survey at the Christian Medical College Hospital in Vellore, South India in 1984, 284 enterobacterial urinary pathogens, along with 102 Salmonellae and 101 Shigellae strains from gastro-intestinal infections, were collected in order to evaluate the incidence of trimethoprim resistance (Young et al, 1986). Studies on beta-lactam antibiotic resistance were conducted on these same clinical isolates and revealed that 80.9% of the urinary pathogens were ampicillin resistant (Minimum Inhibitory Concentration (MIC) > 10mg/L). However, there was a higher incidence of ampicillin resistance (MIC > 10mg/L) amongst the Salmonellae strains (90.2%). Surprisingly, 67 Salmonellae strains were resistant to the second generation cephalosporin, cefuroxime (>8mg/L). In contrast, only a few of these isolates (8) were resistant to the first generation cephalosporin, cephaloridine (MIC > 10mg/L). A study was performed to identify the resistance mechanisms to cefuroxime in these Salmonellae strains.

The cefuroxime resistance determinants were neither transferable nor mobilisable into the standard recipient Escherichia coli J62-2, when selection made on the agar plates containing 8mg/L of the drug. However, the ampicillin resistance determinants were freely transferable. Sensitivity testing of the ampicillin resistant transconjugants revealed that four of them were cefuroxime resistant (MICs = 4 and 8mg/L at culture densities of 10^5 and 10^9 cfu respectively). Both the cefuroxime resistant transconjugants and the original clinical isolates were screened for the type of beta-lactamase production. Isoelectric focusing revealed that all the strains produced an OXA-1 like beta-lactamase, which we have designated OXA-E1. When examined by isoelectric focusing, the main enzymic bands of OXA-E1 and OXA-1 co-focused (pI = 7.4). However, two satellite bands were absent in the OXA-E1 enzyme whereas they were clearly visible in the standard OXA-1 enzyme.

The rates of hydrolysis of various substrates, at fixed concentrations, by both the OXA-E1 and OXA-1 enzymes were analysed under the same experimental conditions. The rates were related to the hydrolysis of penicillin G (i.e. 100%). OXA-E1 and OXA-1 hydrolysed cephaloridine (49.6% and 46.9% respectively), cefotaxime (18.4% and 12.4%) and ampicillin (755% and 573%) to similar extents. However, very significantly, OXA-E1 had a considerably higher activity (8-fold) against cefuroxime than OXA-1 (12.5% and 1.5% respectively). Moreover, the OXA-E1 enzyme could hydrolyse cefoxitin (1.9%) whereas OXA-1 could not. OXA-E1 had higher activity (>2-fold) than OXA-1 against cephalothin (13.0% and 5.8% respectively), cefamandole (39.3% and 15.7%) and nitrocephin (654% and 250%). On the other hand, the OXA-E1 enzyme was less effective than OXA-1 against substrates such as cephradine (0.33% and 3.2%) and carbenicillin (107% and 260%). However, the enzymes shared common inhibitor profiles as they were resistant to clavulanic acid (Dose for 50% inhibition (ID_{50}) >1mM), cloxacillin (ID_{50} = 0.1mM), p-chloromercuribenzoic acid (ID_{50} >1mM), sodium chloride (ID_{50} >10mM), cefoxitin (ID_{50} >1mM) and cefotetan (ID_{50} >1mM).

In conclusion, cefuroxime resistance in these Salmonellae strains was accompanied by the widespread distribution of the novel beta-lactamase OXA-E1. However, other resistance mechanisms may also play a subsidiary role.

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