INTERACTIONS BETWEEN THE BACTERICIDAL EFFECTS OF 4-QUINOLONES AND OTHER GYRASE INHIBITORS ACTING ON *STAPHYLOCOCCI*

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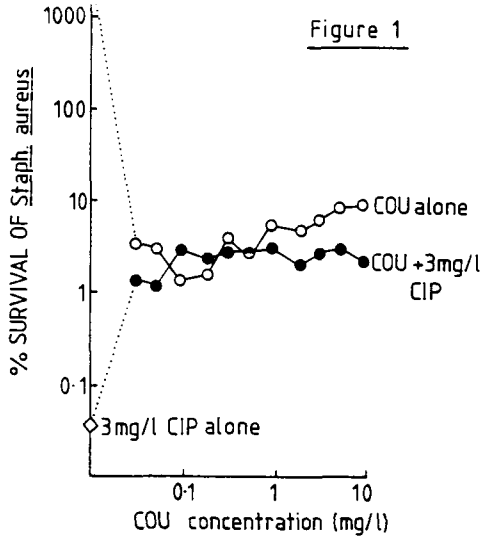
Coumermycin (COU), novobiocin (NOV) and 4-quinolone antibacterials like ciprofloxacin (CIP) and ofloxacin (OFL) inhibit DNA gyrase, which is the only enzyme capable of introducing negative supercoils into DNA (Drlica & Franco 1988). While COU and NOV act on the ß subunits of gyrase the 4-quinolones act principally on the α subunits of this enzyme (Drlica and Franco 1988). In minimum inhibitory concentration (MIC) tests with Staph. aureus COU and CIP were found to act synergistically (Neu et al, 1984). However, in vivo studies have shown that CIP alone was more effective than a combination of CIP and COU in treating Staph. aureus endocarditis in rats (Perrone et al, 1987). To resolve this discrepancy, the bactericidal effects of CIP and COU, alone and in combination against Staphylococci at an initial inoculum size of 10^7 cells mL^{-1}, were studied in nutrient broth at 37°C and survival estimated after 3 hours.



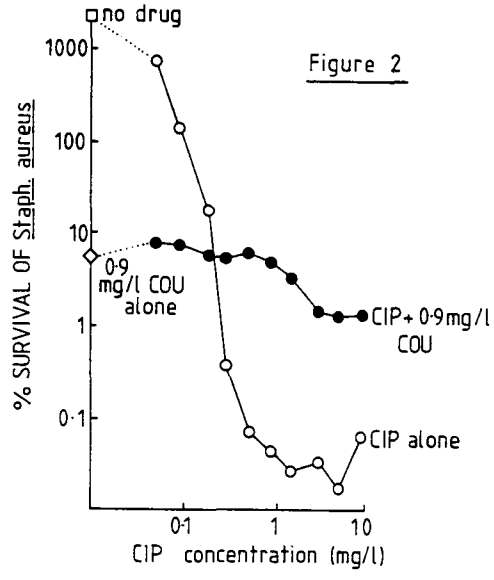


Figure 1 shows that 3mg/L CIP reduced the viable count of Staph. aureus to 0.033% but survival was greater in every mixture tested when increasing concentrations of COU were combined with 3mg/L CIP. Antagonism was also seen when increasing concentrations of CIP were combined with 0.9 mg/L COU (Fig. 2). At CIP concentrations above 0.2mg/l survival in the mixtures was more than 10 fold to up to 100 fold higher than that seen with CIP alone. Similar results were found when NOV or COU were combined with CIP or OFL to treat Staph. aureus or Staph. warneri, so the phenomenon seems to be a general one. These results agree with the in vivo findings of Perrone et al (1987) and disagree with the MIC data of Neu et al (1984). Since MIC studies solely estimate the bacteriostatic effects of 4-quinolones (Smith, 1984), clinical resolution of infections would seem to depend more on bacterial kill than on suppression of bacterial multiplication. Thus bactericidal investigations of mixtures of these two different classes of gyrase inhibitors provide a better prediction of clinical effects than MIC studies.

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Smith, J.T. (1984) Pharm. J. 233: 299-305