NORFLOXACIN HAS A NOVEL BACTERICIDAL MECHANISM UNRELATED TO THAT OF OTHER 4-QUINOLONES

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In nutrient broth the most bactericidal concentrations of ciprofloxacin and ofloxacin exhibit a rifampicin-resistant bactericidal mechanism, termed B, in addition to a rifampicin-sensitive mechanism, termed A. It was found that mechanism A was the only bactericidal mechanism exerted by nalidixic acid, oxolinic acid, norfloxacin and five other 4-quinolone antibacterials investigated at their most bactericidal concentrations in nutrient broth (Ratcliffe and Smith, 1984).

Novobiocin is chemically unrelated to the 4-quinolone antibacterials but it acts on the same target site as the 4-quinolones : DNA gyrase. However, while novobiocin is believed to act on the B subunit of this enzyme, the 4-quinolones are considered to act on the A subunit of DNA gyrase (Cozzarelli, 1980).

An investigation was undertaken to test if the bactericidal mechanisms possessed by ciprofloxacin and ofloxacin could be related to that of novobiocin. When the effects of novobiocin, nalidixic and oxolinic acids were tested on phosphate-buffered normal saline suspensions of E. coli KL16, it was found they did not kill such non-dividing bacteria, whereas the drugs were bactericidal in nutrient broth (Table). However, ciprofloxacin and ofloxacin did kill non-dividing bacteria (Table). This may have occurred because ciprofloxacin and ofloxacin uniquely possess mechanism B and suggests that novobiocin, like nalidixic and oxolinic acids, does not exert such a killing mechanism.

Table

	mg/l	Time (min) taken to kill 50% of E. coli KL16 NUTRIENT BROTH	PHOSPHATE BUFFERED SALINE
Novobiocin	900	76	Bacteriostasis
Nalidixic acid	90 *	16	Bacteriostasis
Oxolinic acid	0.9 *	14	Bacteriostasis
Ciprofloxacin	0.15*	6	21
Ofloxacin	0.9 *	6	12
Norfloxacin	1.5 *	11	70

* = most bactericidal concentration.

However, norfloxacin was surprisingly found to exhibit an ability to kill non-dividing E. coli (Table). A similar observation has also been reported by Zeiler and Grohe (1984). This novel bactericidal activity of norfloxacin would hence seem to be unrelated to mechanism B of ciprofloxacin and ofloxacin because in nutrient broth containing rifampicin, norfloxacin is devoid of bactericidal activity (Ratcliffe and Smith, 1984). Recently it has been shown in vitro that norfloxacin can bind to DNA with a greater affinity than that of any other 4-quinolone including ciprofloxacin, and the binding of norfloxacin to DNA occurs in the absence of DNA gyrase (Shen and Pernet, 1985). This finding may suggest that the novel bactericidal mechanism of norfloxacin we describe can only take place when gyrase is not associated with DNA (as would occur in non-dividing bacteria) but could not function when gyrase becomes associated with DNA, which is the situation applicable to nutrient broth cultures.

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