THE BACTERICIDAL ACTION OF NALIDIXIC ACID CAN BE POTENTIATED BY AMINOGLYCOSIDES

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The bactericidal activity of nalidixic acid can only occur when bacteria are able to synthesize RNA and protein (Deitz et al, 1966) hence bacterial killing by the drug can be antagonized by the addition of a bacteriostatic concentration of rifampicin or chloramphenicol, respectively (Smith, 1984). The aminoglycoside antibiotics also inhibit bacterial protein synthesis and because of this it would seem they too should antagonize the action of nalidixic acid. However, aminoglycosides have recently been discovered to possess another mechanism that operates at concentrations less than those inhibiting protein synthesis. This extra mechanism that takes place at such low concentrations interferes with the initiation of DNA synthesis (Tanaka et al, 1984). As nalidixic acid's target site is also associated with DNA metabolism this study was undertaken to test whether the two classes of drugs could interact.

Concentrations of antibacterials which only slightly reduced the multiplication of Escherichia coli KL16 were determined, then their effects on bacterial survival in the presence of 50µg/ml of nalidixic acid were assessed in nutrient broth that initially contained about 10^7 colony forming units per ml.

Table

Other drugs	µg/ml	Time (min.) taken to kill 99% of the E.coli		CHANGE (min.) caused by other drug
		Nalidixic acid alone	Nalidixic acid + other drug	
rifampicin	10	128	252	+124
chloramphenicol	1	141	175	+ 34
tetracycline	0.3	142	260	+118
streptomycin	2	153	130	- 23
gentamicin	0.2	163	116	- 47
kanamycin	0.8	156	106	- 50
netilmicin	0.4	142	86	- 56
tobramycin	0.4	191	98	- 93
amikacin	0.4	168	127	- 41
sisomicin	0.4	127	72	- 55

The table shows that even the subinhibitory concentration of rifampicin tested reduced the bactericidal activity of nalidixic acid, which can be explained by rifampicin partially inhibiting the rate of RNA synthesis. The same was true with chloramphenicol and tetracycline which could mediate their antagonism of nalidixic acid via a partial inhibition of protein synthesis.

However, all seven aminoglycosides increased the rate of kill caused by nalidixic acid; the average reduction being 52 minutes which is about 33% more rapid than the average rate of kill caused by nalidixic acid alone. These results can be explained by the aminoglycosides acting at their subinhibitory concentrations to impair the initiation of DNA synthesis which could react synergistically with the action of nalidixic acid on DNA metabolism. This synergy may have clinical relevance in the treatment of patients with impaired immune responses where a greater bactericidal effect is desirable.

Deitz, W.H. et al (1966) Journal of Bacteriology 91 : 768-773.
Smith, J.T. (1984) Pharmaceutical Journal 233 : 299-305.
Tanaka et al (1984) Biochem. Biophys. Res. Commun. 122 : 460-465.